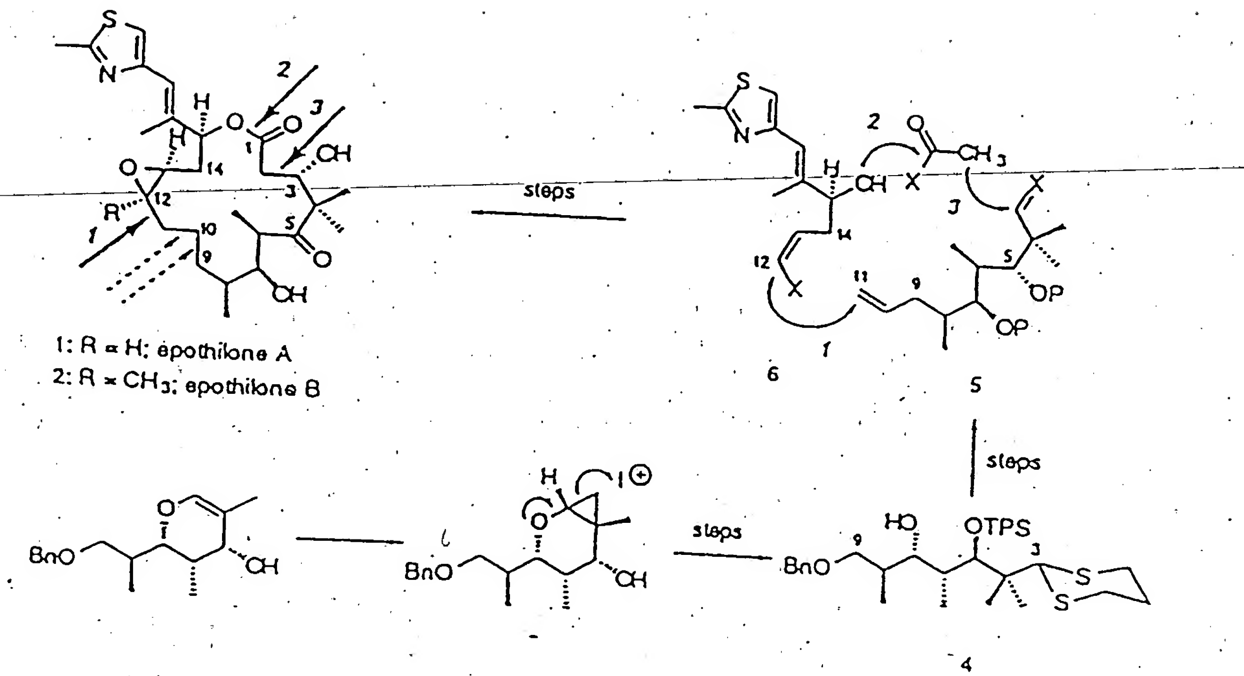
(A)


steps
1: R = H: epothilone A
2: R = CH3: epothilone B
6
5
steps
BnO
OTPS
4

(B)

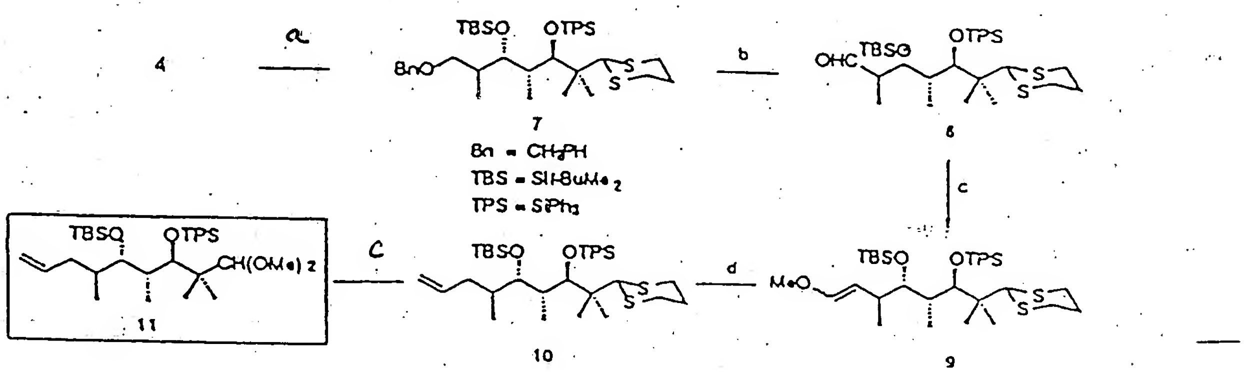

4
a
7
b
8
c
d
9
10
c
11
Bn = CH2PH
TBS = SiI-BuMe2
TPS = SiPh3

Figure 1

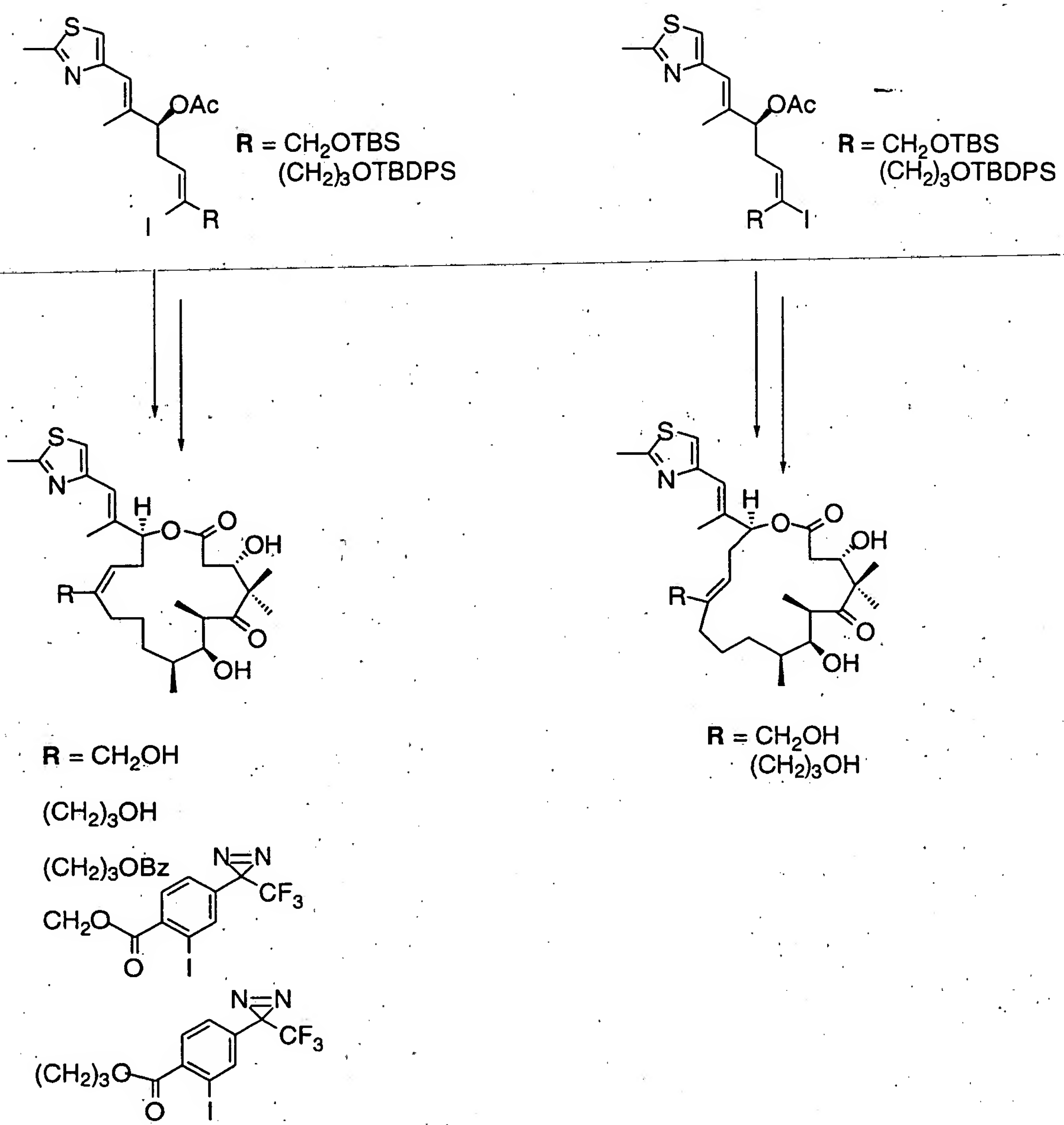
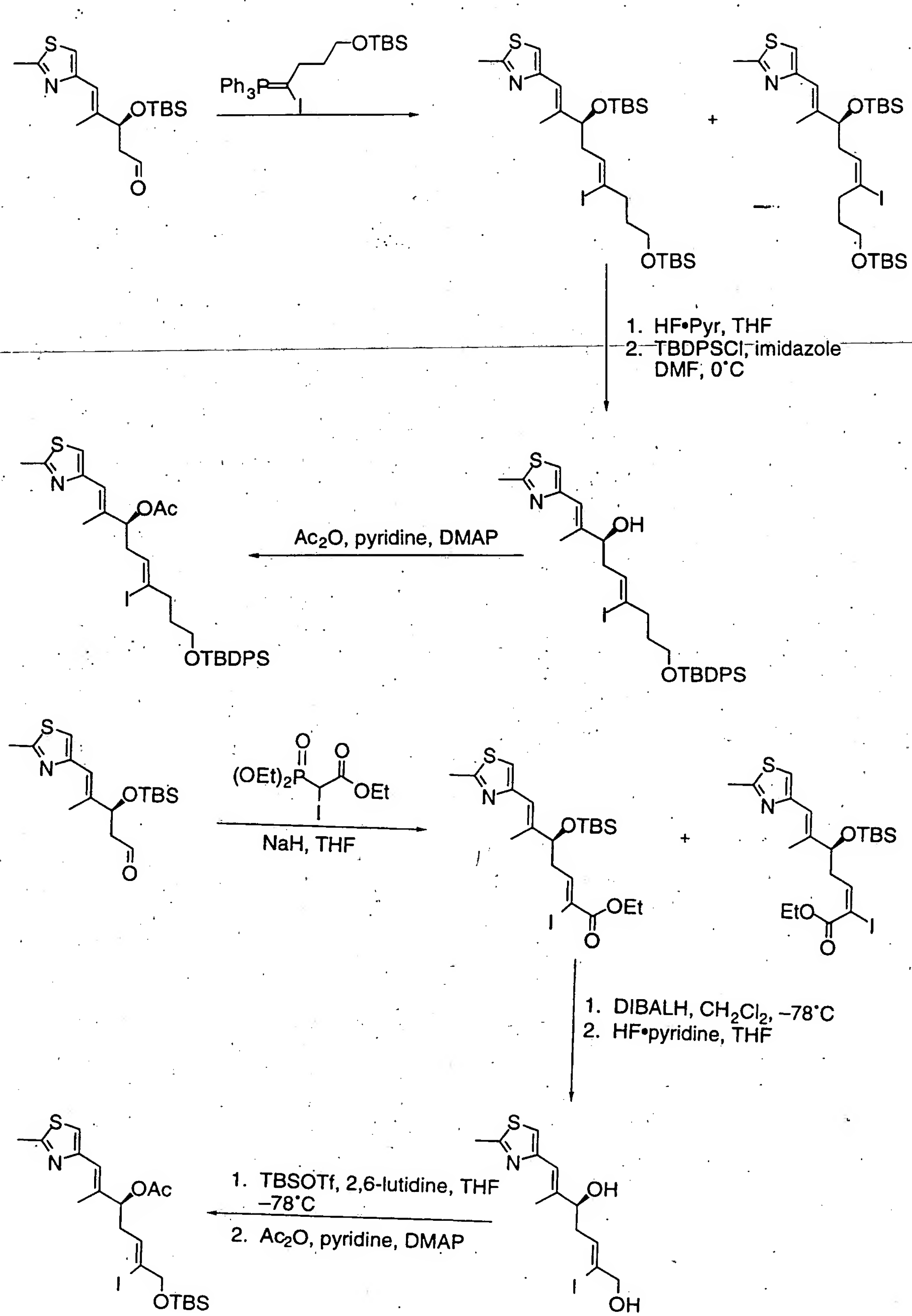

OAc
R = CH2OTBS
(CH2)3OTBDPS
R = CH2OH
(CH2)3OH
(CH2)3OBz
CF3
CH2O
(CH2)3O

Figure 2



Ph3P
OTBS
1. HF•Pyr, THF
2. TBDPSCl, imidazole DMF, 0°C
OTBDPS
Ac2O, pyridine, DMAP
(OEt)2P
OEt
NaH, THF
1. DIBALH, CH2Cl2, –78°C
2. HF•pyridine, THF
1. TBSOTf, 2,6-lutidine, THF –78°C
2. Ac2O, pyridine, DMAP

Figure 3(A)

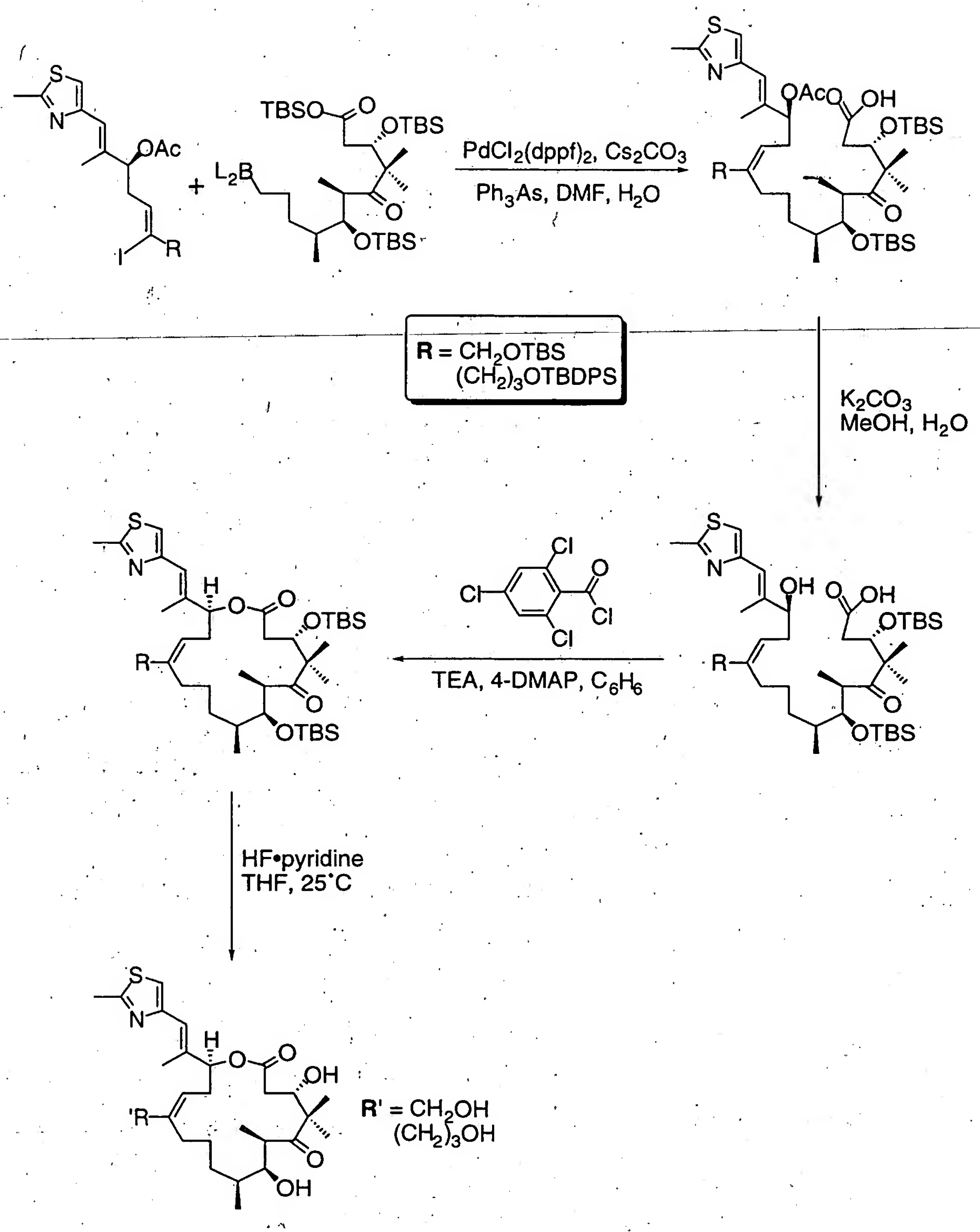

S
N
OAc
I
R
TBSO
O
OTBS
L2B
O
OTBS
PdCl2(dppf)2, Cs2CO3
Ph3As, DMF, H2O
OAc
O
OH
OTBS
R
O
OTBS
R = CH2OTBS
(CH2)3OTBDPS
K2CO3
MeOH, H2O
OH
O
OH
OTBS
R
O
OTBS
Cl
O
Cl
Cl
Cl
TEA, 4-DMAP, C6H6
H
O
O
OTBS
R
O
OTBS
HF•pyridine
THF, 25°C
H
O
O
OH
'R
O
OH
R' = CH2OH
(CH2)3OH

Fig. 3(B)

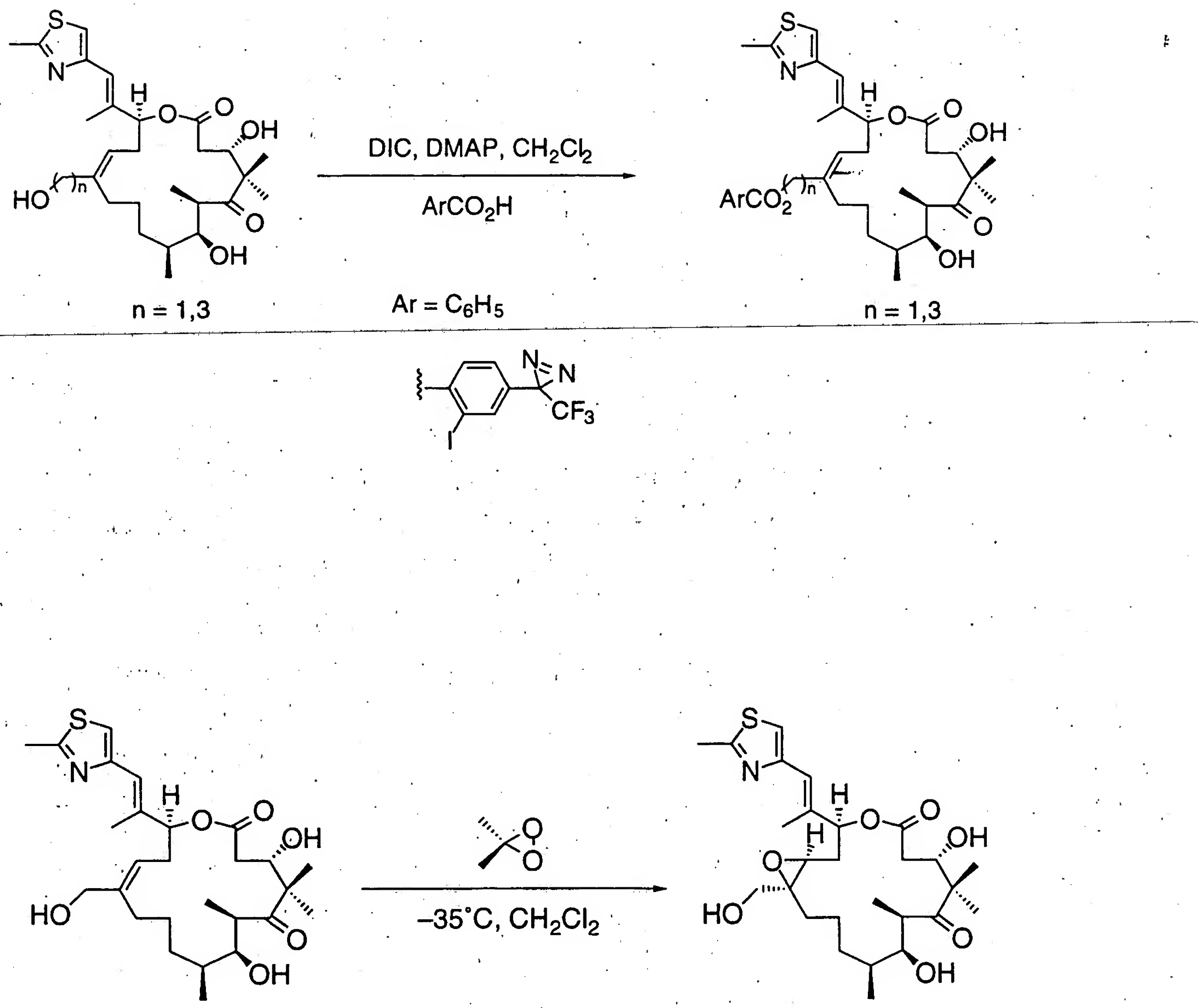


Fig. 3(C)

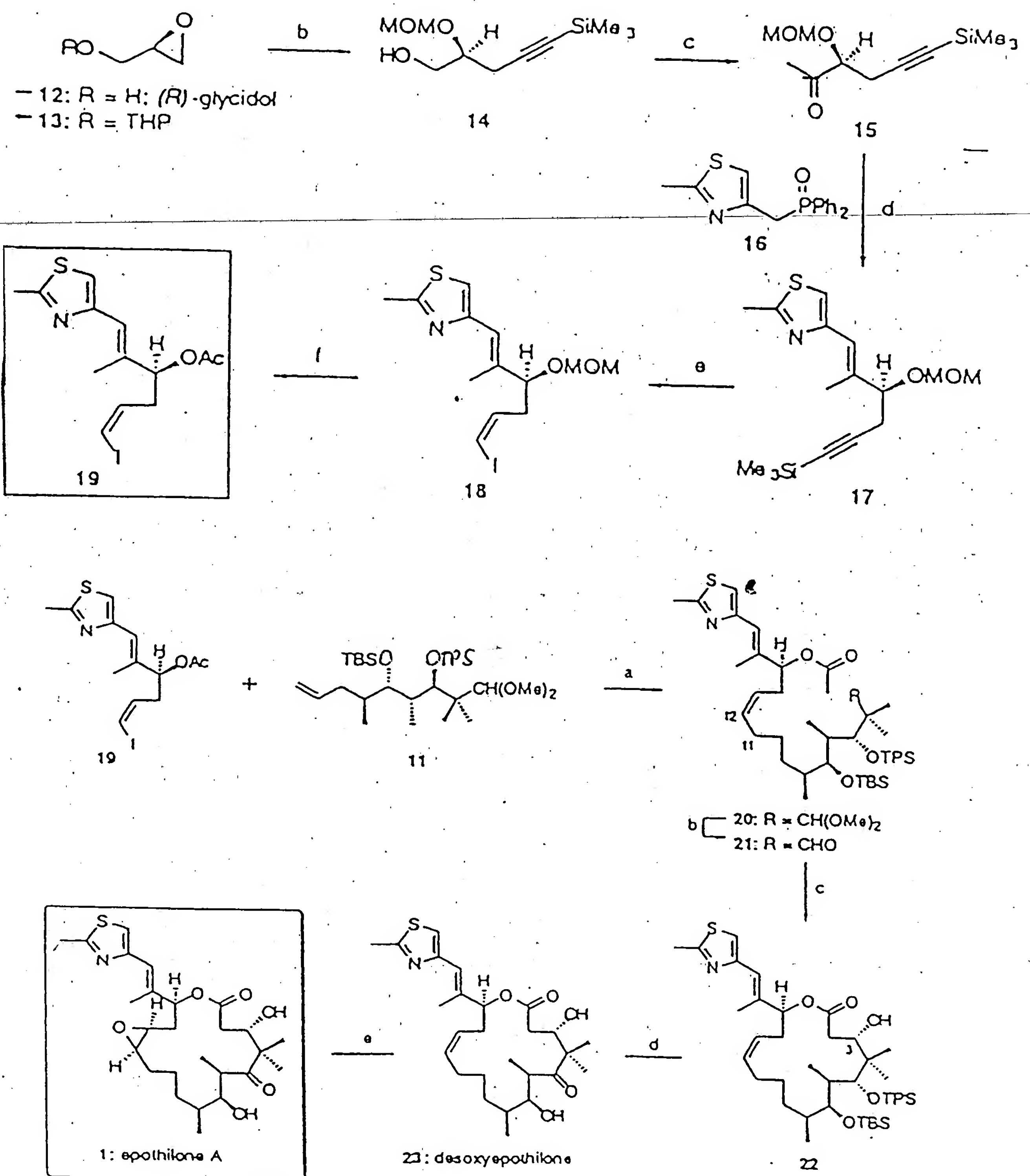

RO
12: R = H: (R)-glycidol
13: R = THP
b
MOMO
HO
H
SiMe3
14
c
15
PPh2
16
d
17
OMOM
Me3Si
e
18
f
OAc
19
TBSO
OTPS
CH(OMe)2
11
a
OTPS
OTBS
20: R = CH(OMe)2
21: R = CHO
22
23: desoxyepothilone
1: epothilone A

Figure 4

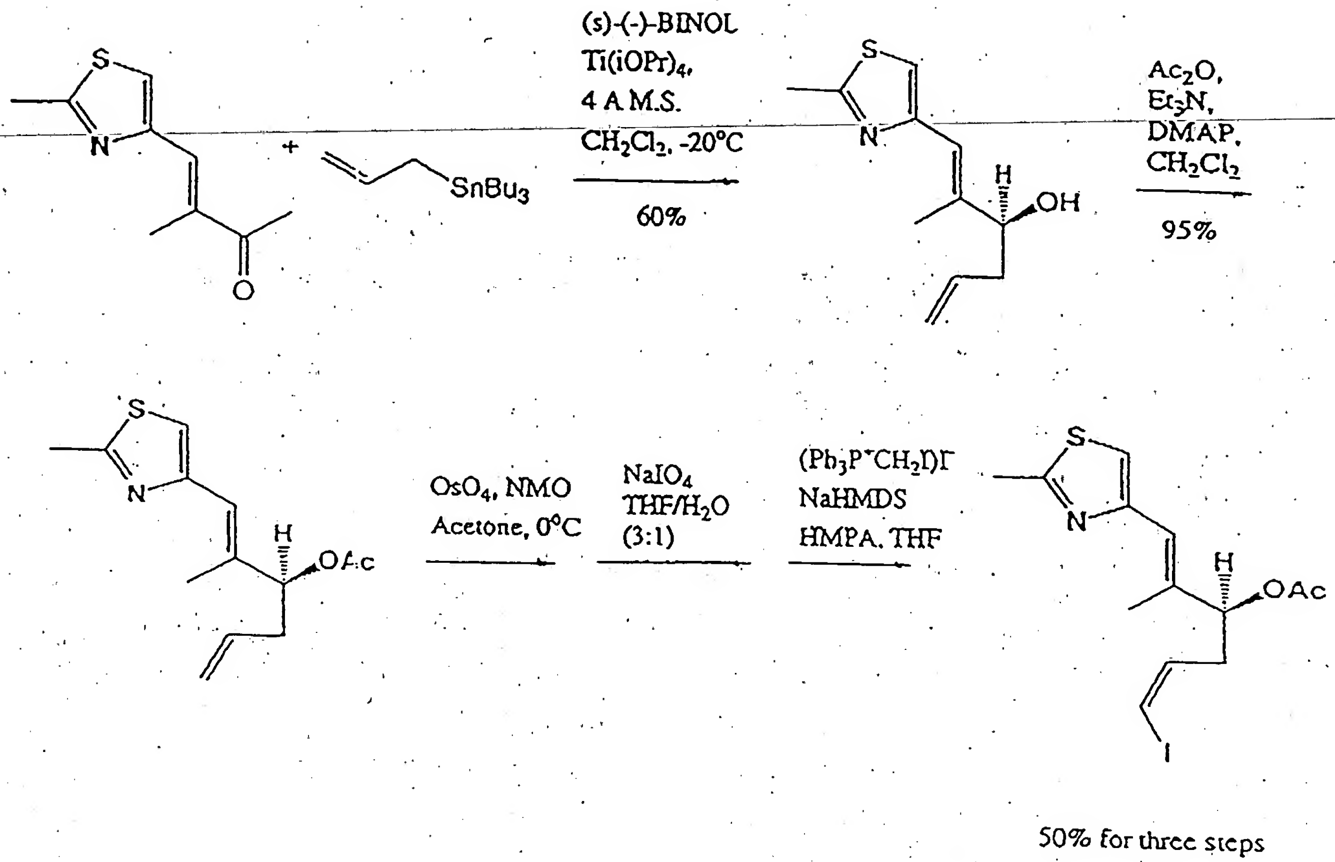
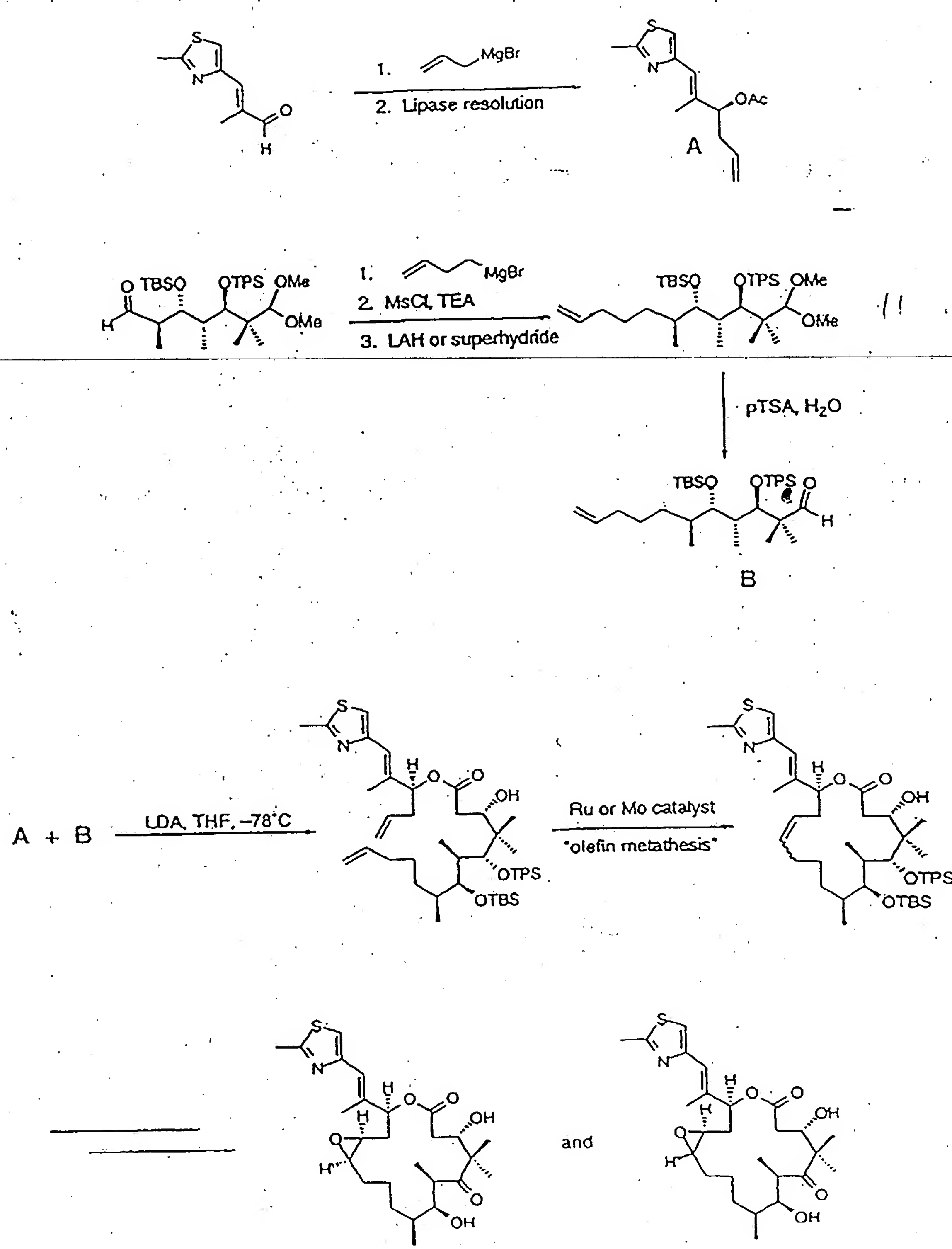

(s)-(-)-BINOL
Ti(iOPr)4,
4 A M.S.
CH2Cl2, -20°C
60%
SnBu3
OH
Ac2O,
Et3N,
DMAP,
CH2Cl2
95%
OAc
OsO4, NMO
Acetone, 0°C
NaIO4
THF/H2O
(3:1)
(Ph3P+CH2I)I-
NaHMDS
HMPA, THF
50% for three steps

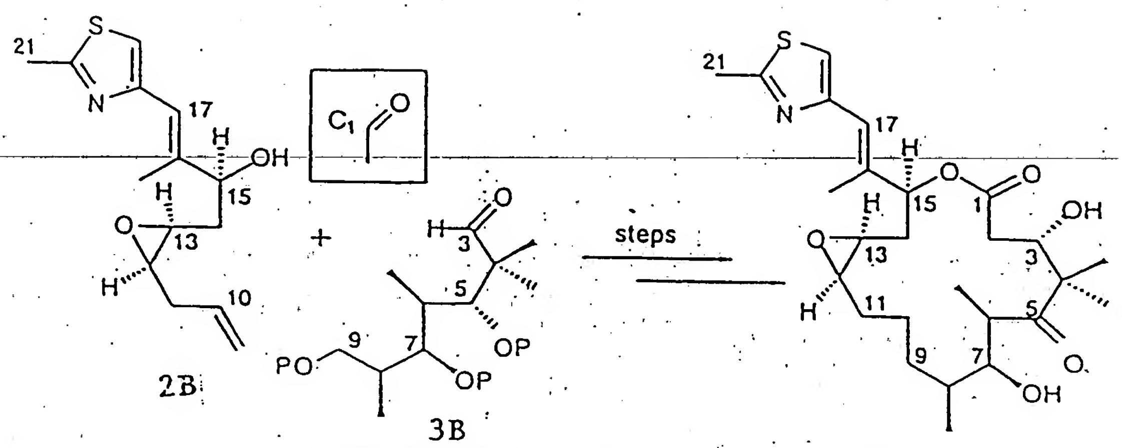
Figure 5



cis epoxide (epothilone A) *trans* epoxide (epothilone analog)

*17 steps from known starting materials vs. 27 steps for aldol macrocyclization

Figure 6

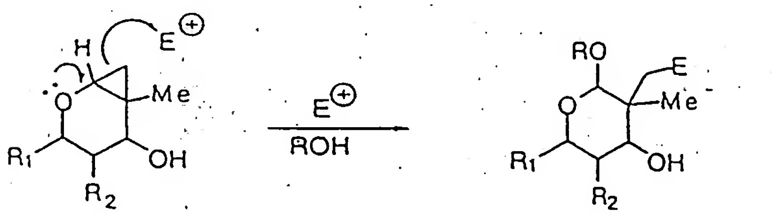


2B 3B

P = unspecified protecting group

1 : epothilone A

Convergent strategy for a total synthesis of epothilone A (1).

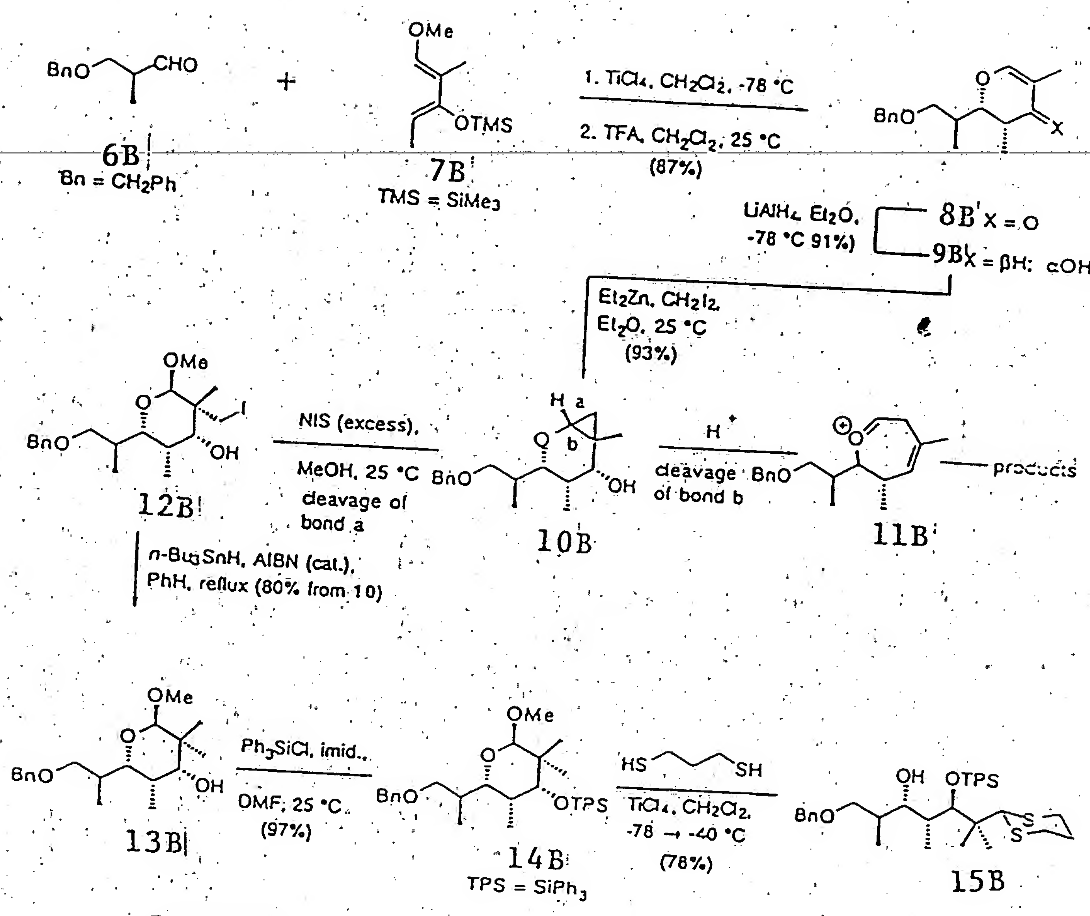


4B

5B E = H or E = X— H

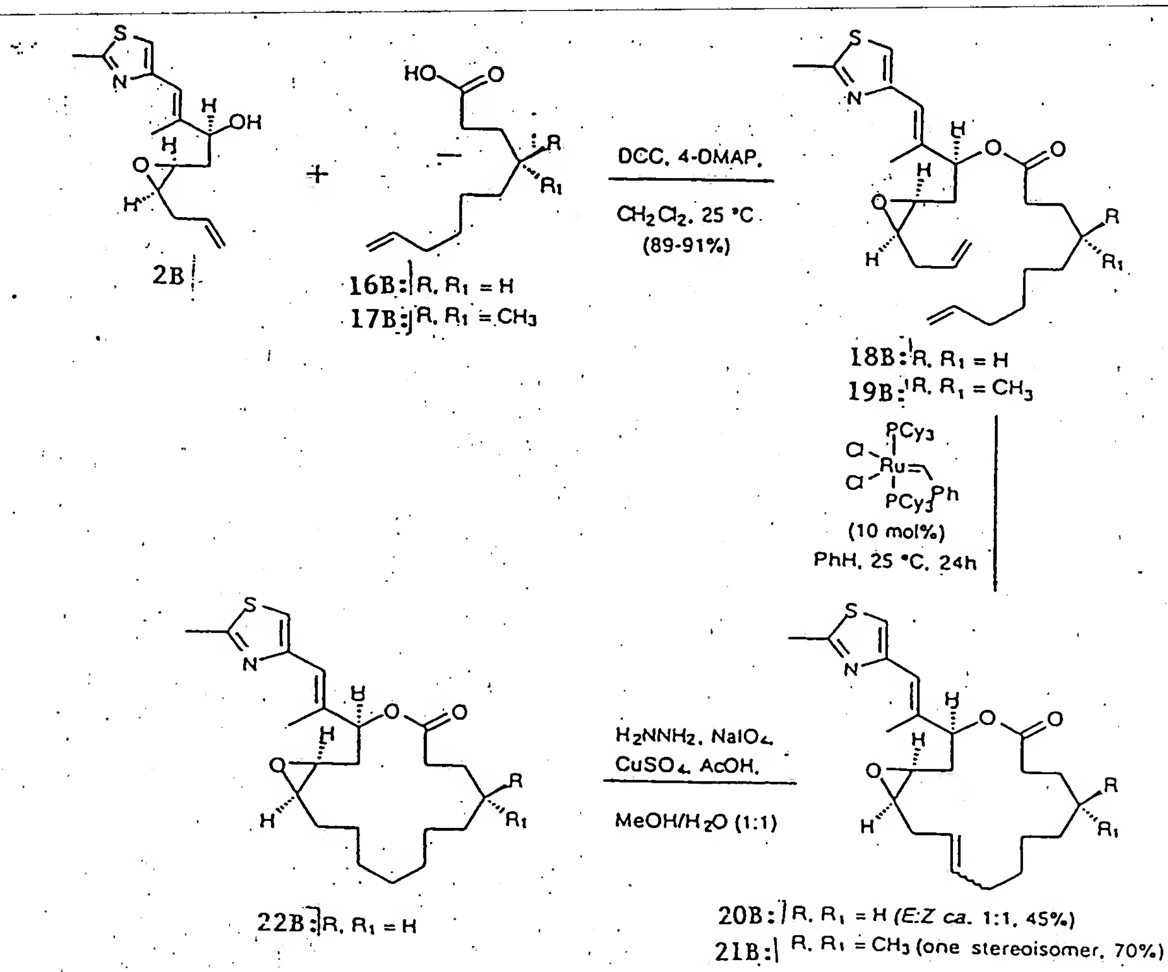
The glycal cyclopropane solvolysis strategy for the introduction of geminal methyl groups.

Figure 7



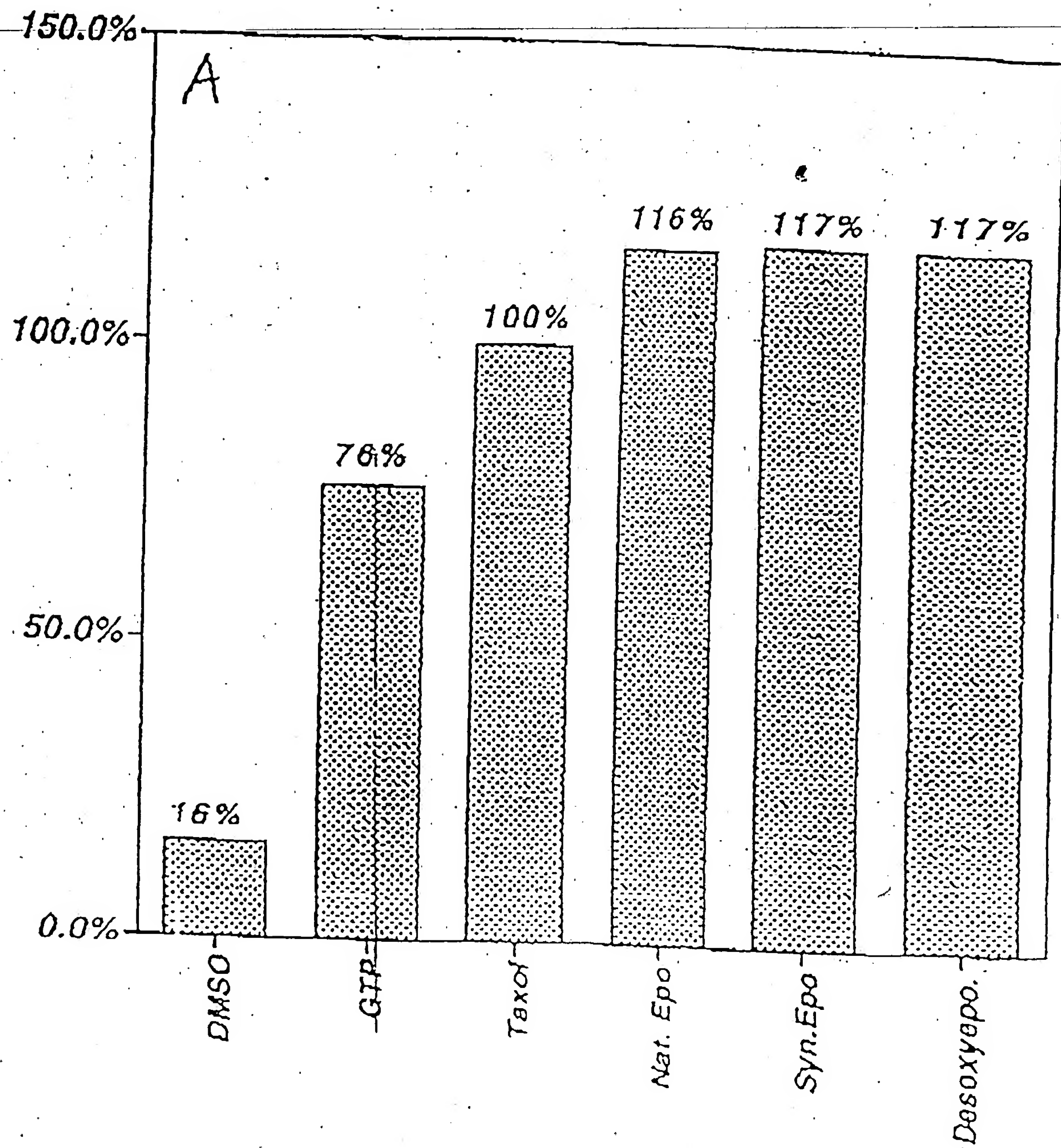
Enantioselective synthesis of compound 15B

Figure 8



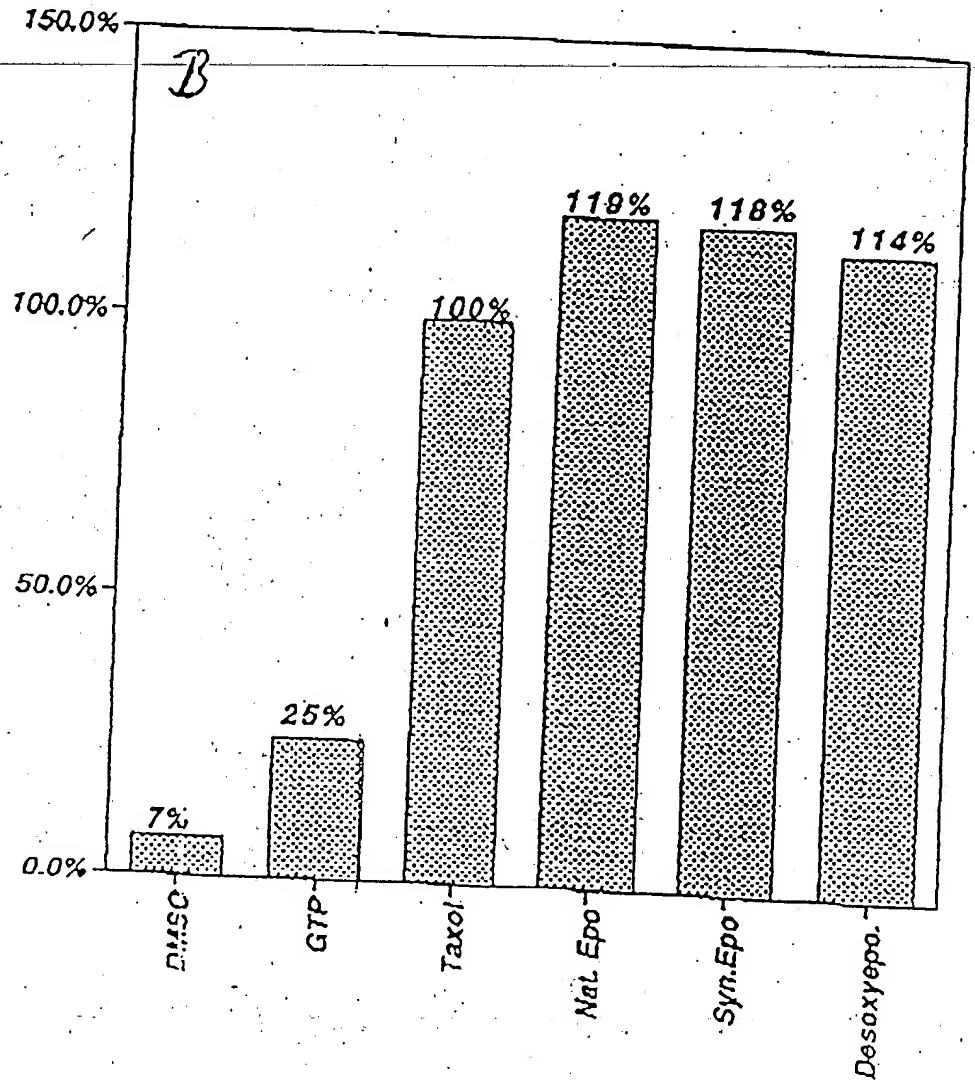
Construction of epothilone model systems 20^B, 21^B, and 22^B by ring-closing olefin metathesis

Figure 9



150.0%
100.0%
50.0%
0.0%
A
16%
76%
100%
116%
117%
117%
DMSO
GTP
Taxol
Nat. Epo
Syn.Epo
Desoxyepo.

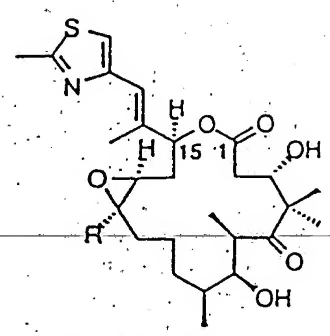
Figure 10



150.0%
100.0%
50.0%
0.0%
B
7%
25%
100%
118%
118%
114%
DMSO
GTP
Taxol
Nat. Epo
Syn.Epo
Desoxyepo.

Figure 11

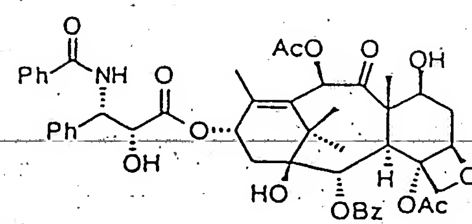
(A)



R = H; epothilone A

R = CH_3; epothilone B

(B)



1A: taxol™

Figure 12

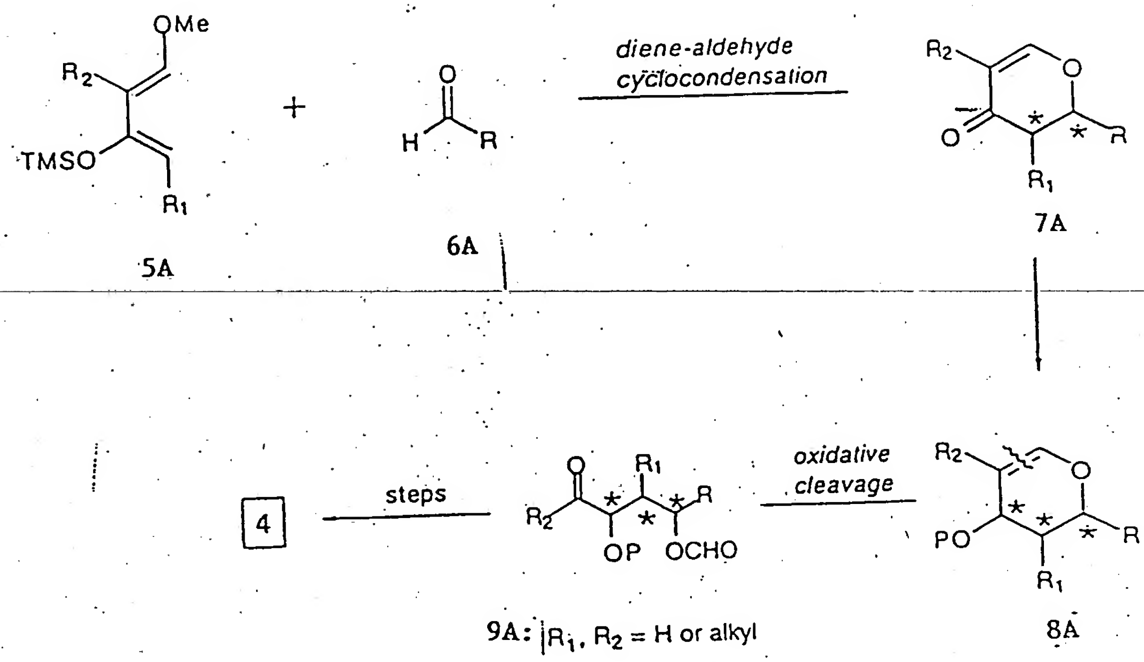

OMe
R2
TMSO
R1
5A
+
O
H
R
6A
diene-aldehyde
cyclocondensation
R2
O
O
R
R1
7A
4
steps
O
R1
R
R2
OP
OCHO
9A: R1, R2 = H or alkyl
oxidative
cleavage
R2
O
PO
R
R1
8A

Figure 13

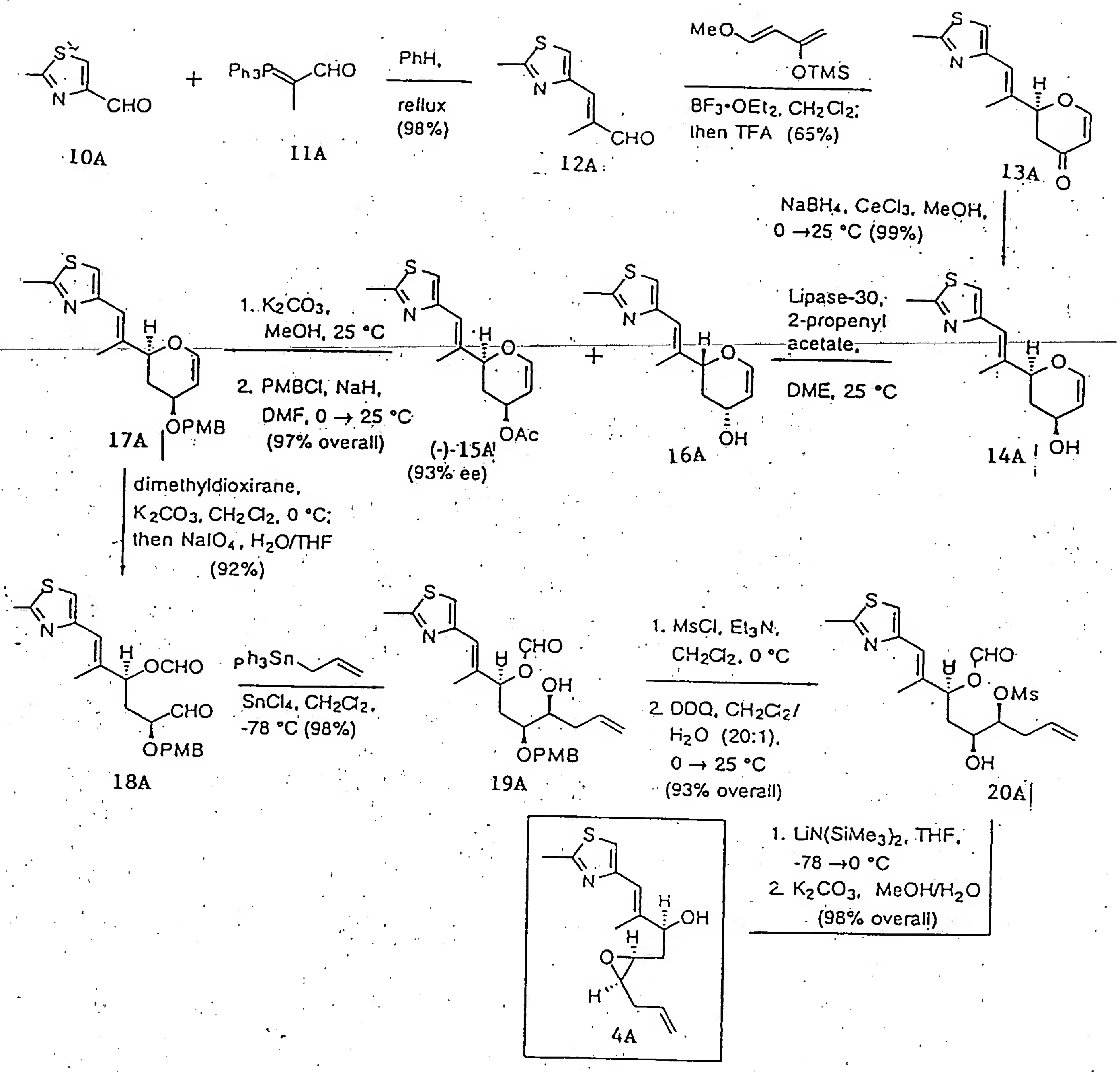

10A
11A
PhH,
reflux
(98%)
12A
BF3·OEt2, CH2Cl2;
then TFA (65%)
13A
NaBH4, CeCl3, MeOH,
0 →25 °C (99%)
14A
Lipase-30,
2-propenyl
acetate,
DME, 25 °C
16A
(-)-15A
(93% ee)
1. K2CO3,
MeOH, 25 °C
2. PMBCl, NaH,
DMF, 0 → 25 °C
(97% overall)
17A
dimethyldioxirane,
K2CO3, CH2Cl2, 0 °C;
then NaIO4, H2O/THF
(92%)
18A
SnCl4, CH2Cl2,
-78 °C (98%)
19A
1. MsCl, Et3N,
CH2Cl2, 0 °C
2. DDQ, CH2Cl2/
H2O (20:1),
0 → 25 °C
(93% overall)
20A
1. LiN(SiMe3)2, THF,
-78 →0 °C
2. K2CO3, MeOH/H2O
(98% overall)
4A

Figure 14

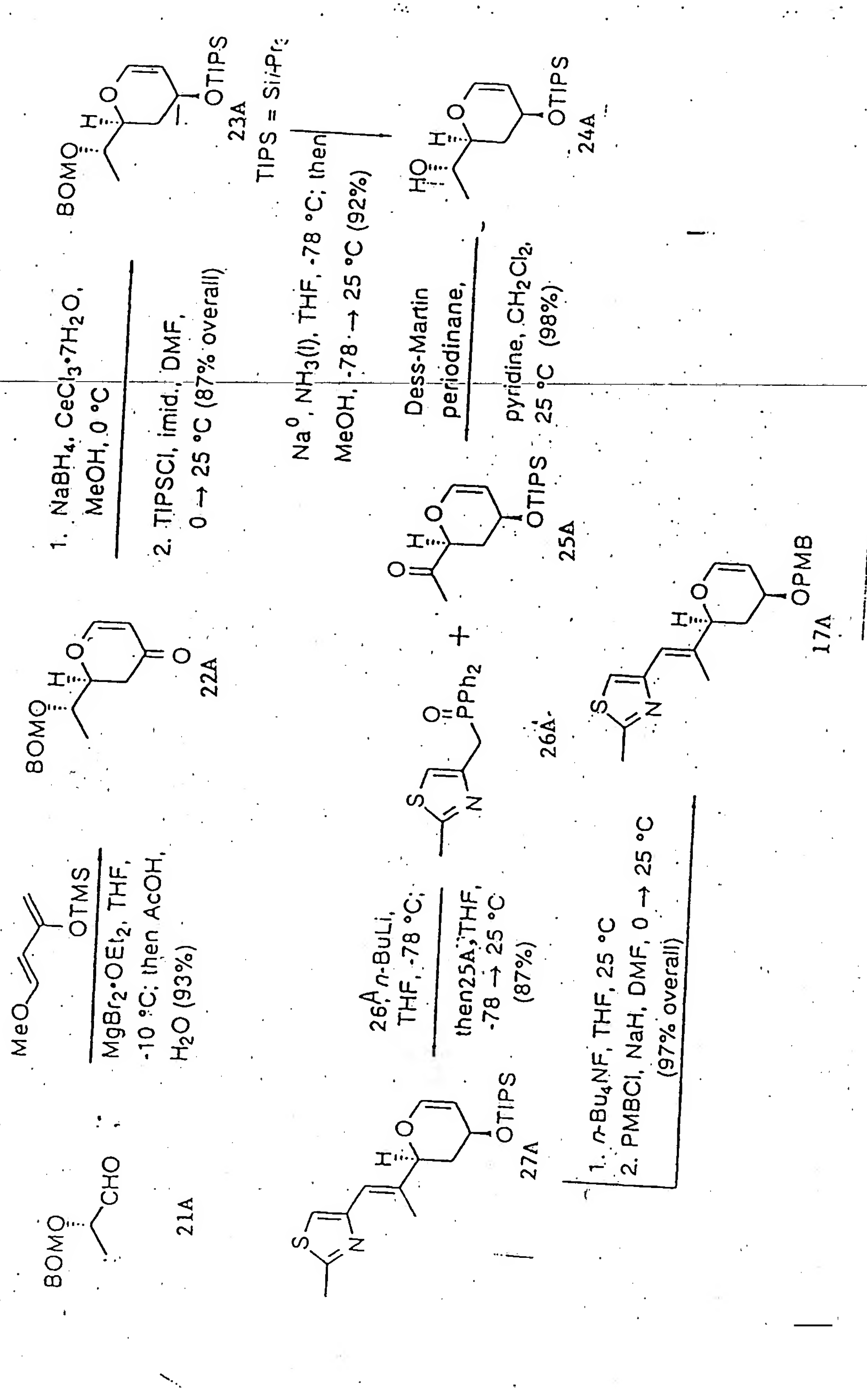


Figure 15

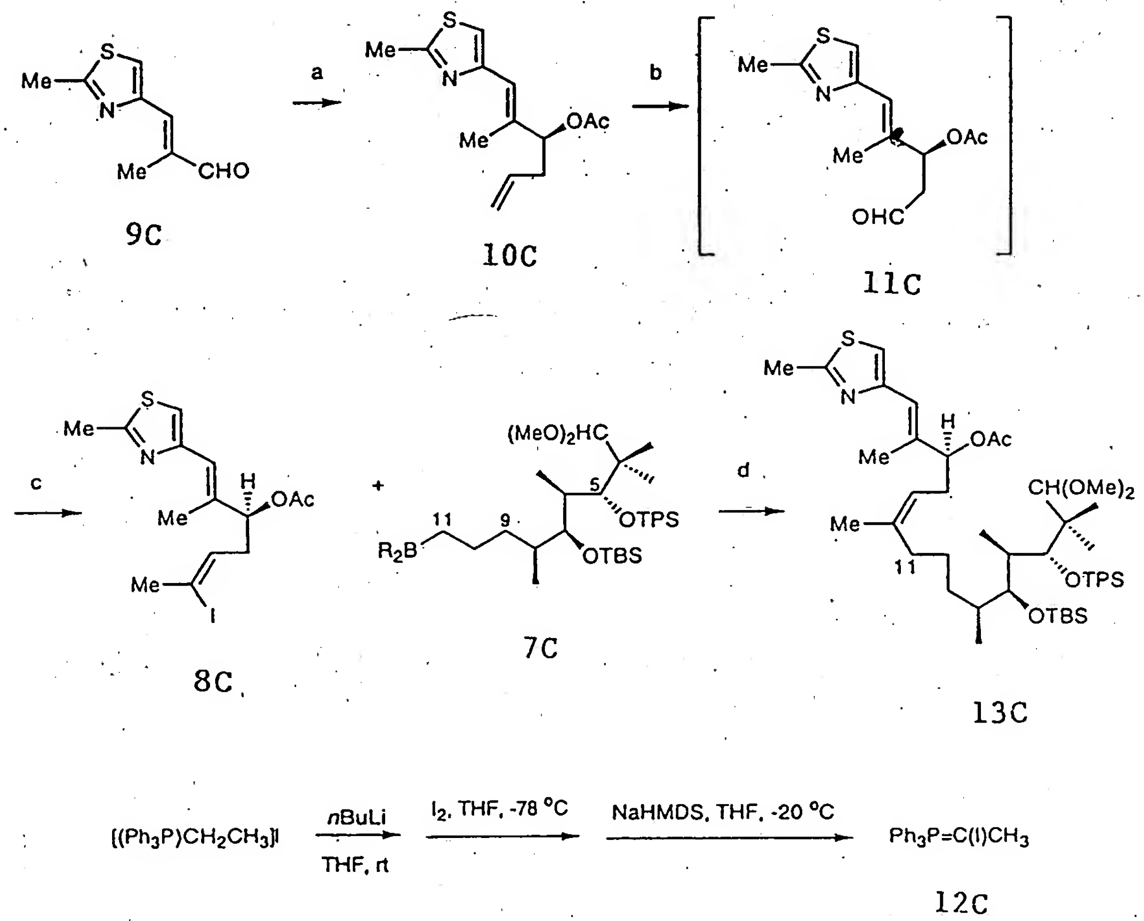

a
b
c
d
9C
10C
11C
8C
7C
13C
[(Ph3P)CH2CH3]I
nBuLi
THF, rt
I2, THF, -78 °C
NaHMDS, THF, -20 °C
Ph3P=C(I)CH3
12C

Figure 16

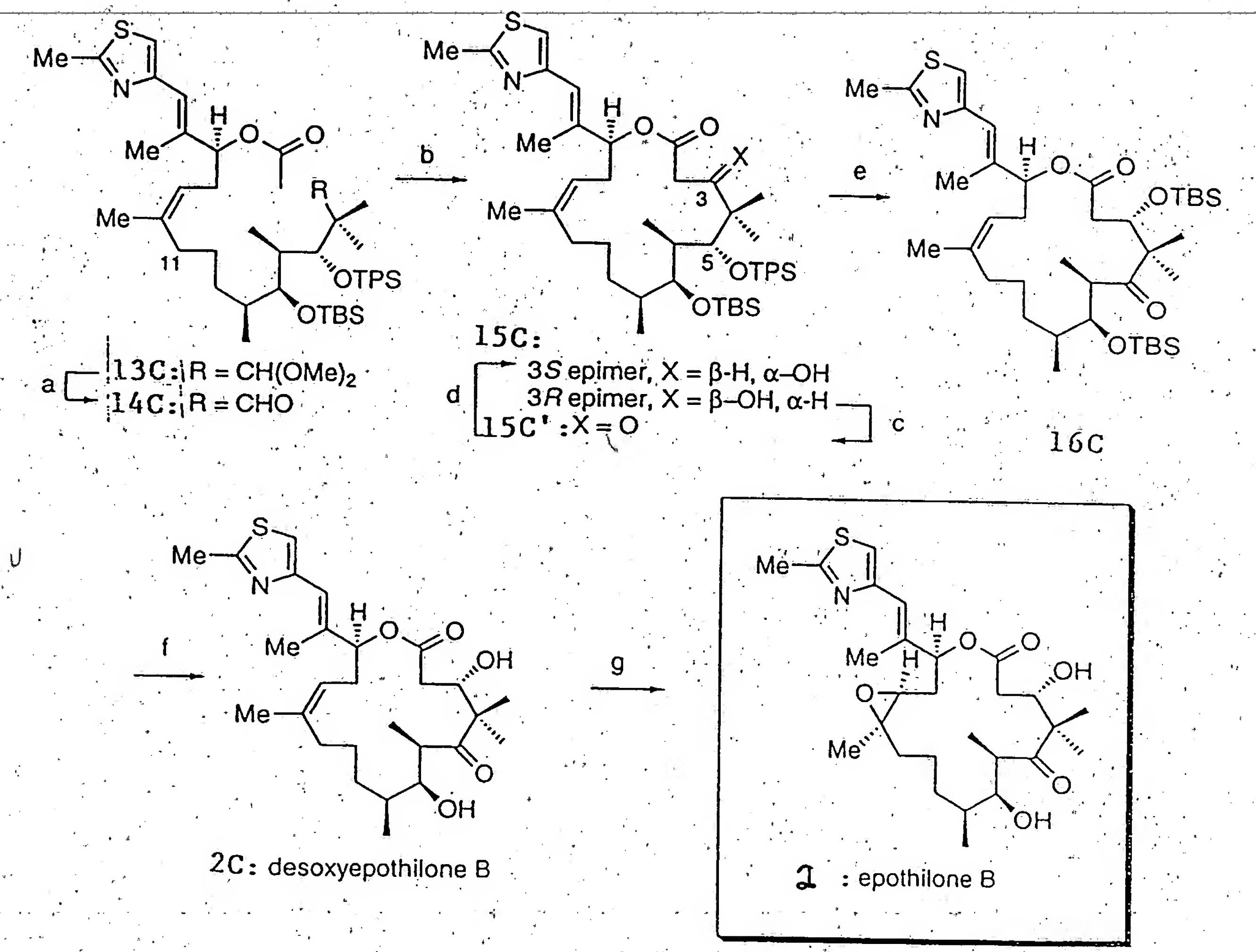
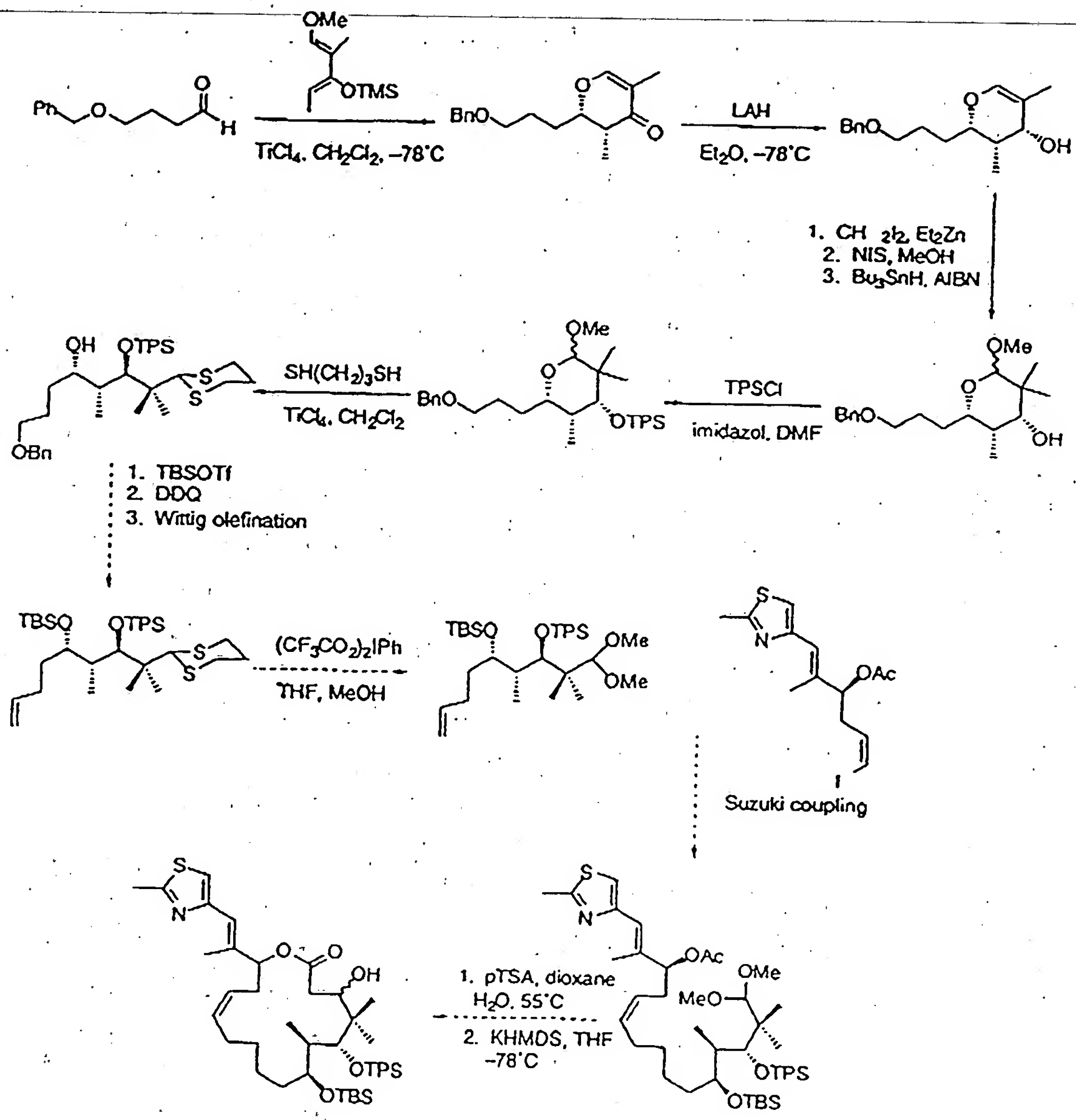

13C: R = CH(OMe)2
14C: R = CHO
15C:
3S epimer, X = β-H, α-OH
3R epimer, X = β-OH, α-H
15C' : X = O
16C
2C: desoxyepothilone B
1 : epothilone B

Figure 17



OMe
OTMS
Ph
O
H
TiCl4, CH2Cl2, -78°C
BnO
LAH
Et2O, -78°C
OH
1. CH2I2, Et2Zn
2. NIS, MeOH
3. Bu3SnH, AIBN
OMe
TPSCl
imidazol, DMF
OTPS
SH(CH2)3SH
TiCl4, CH2Cl2
OH
OBn
1. TBSOTf
2. DDQ
3. Wittig olefination
TBSO
(CF3CO2)2IPh
THF, MeOH
OAc
Suzuki coupling
1. pTSA, dioxane H2O, 55°C
2. KHMDS, THF -78°C
MeO
OTBS

Figure 18

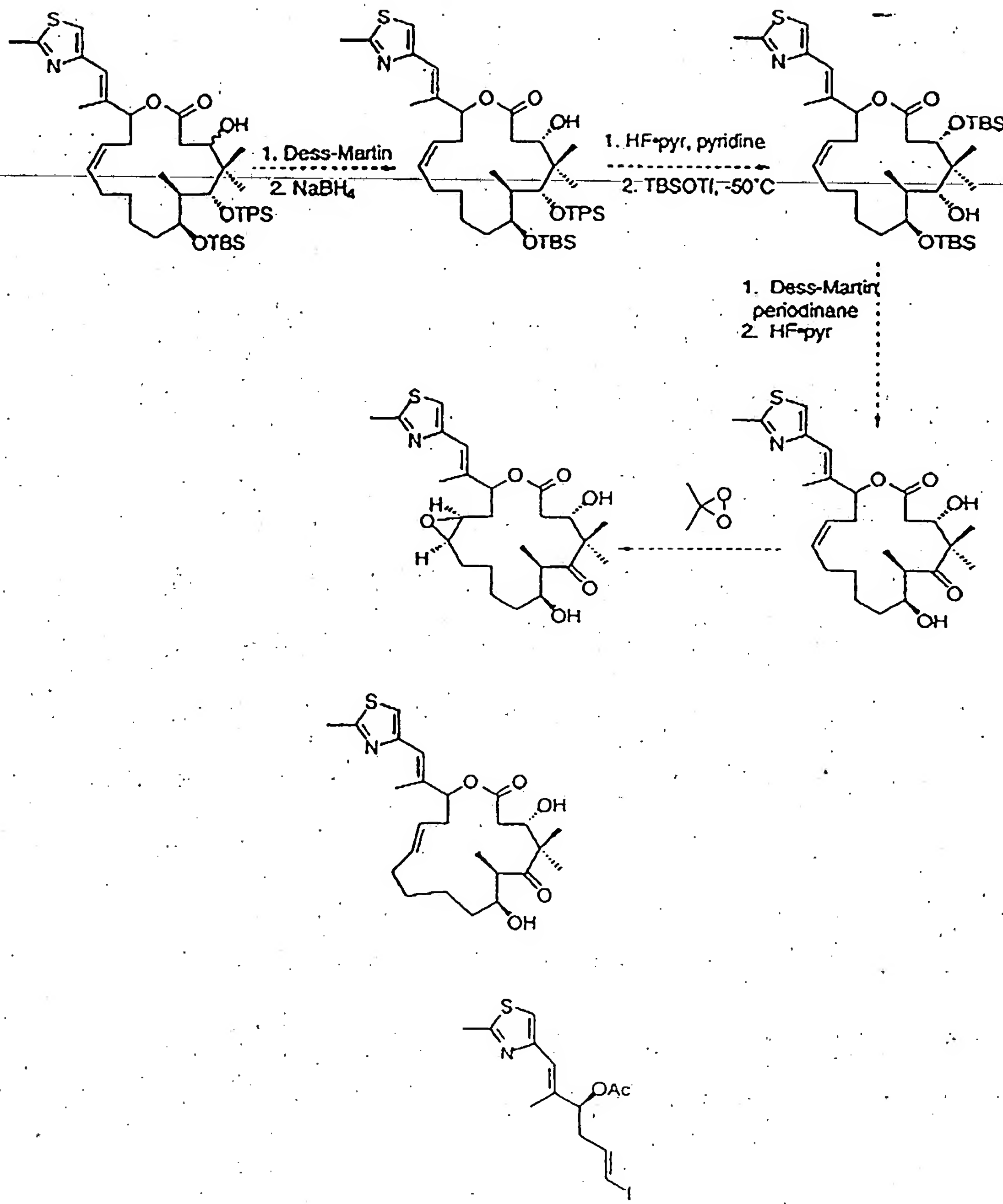
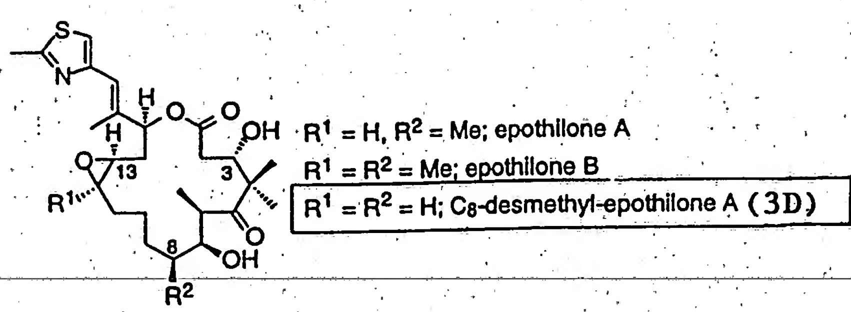
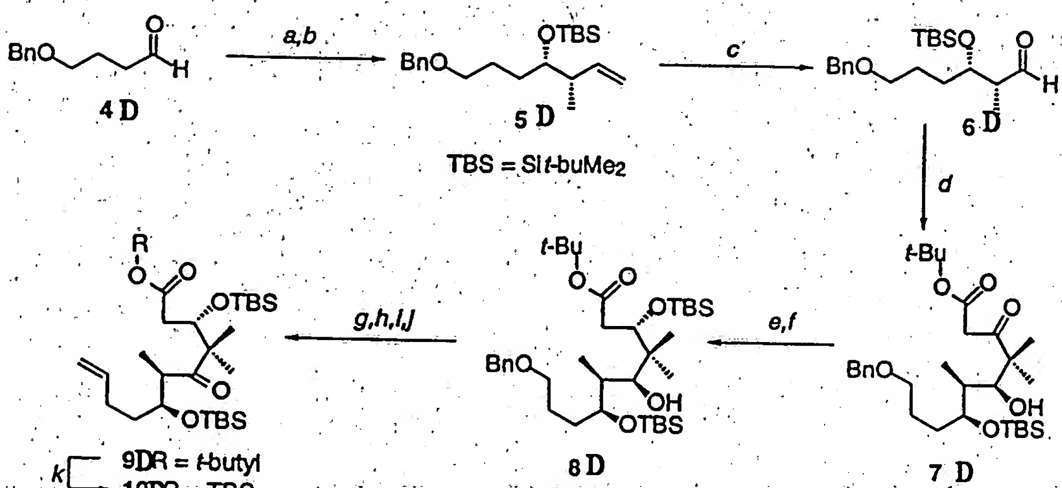

1. Dess-Martin
2. NaBH4
1. HF•pyr, pyridine
2. TBSOTf, -50°C
1. Dess-Martin periodinane
2. HF•pyr
OH
OTPS
OTBS
OTBS
OH
OAc

Figure 19

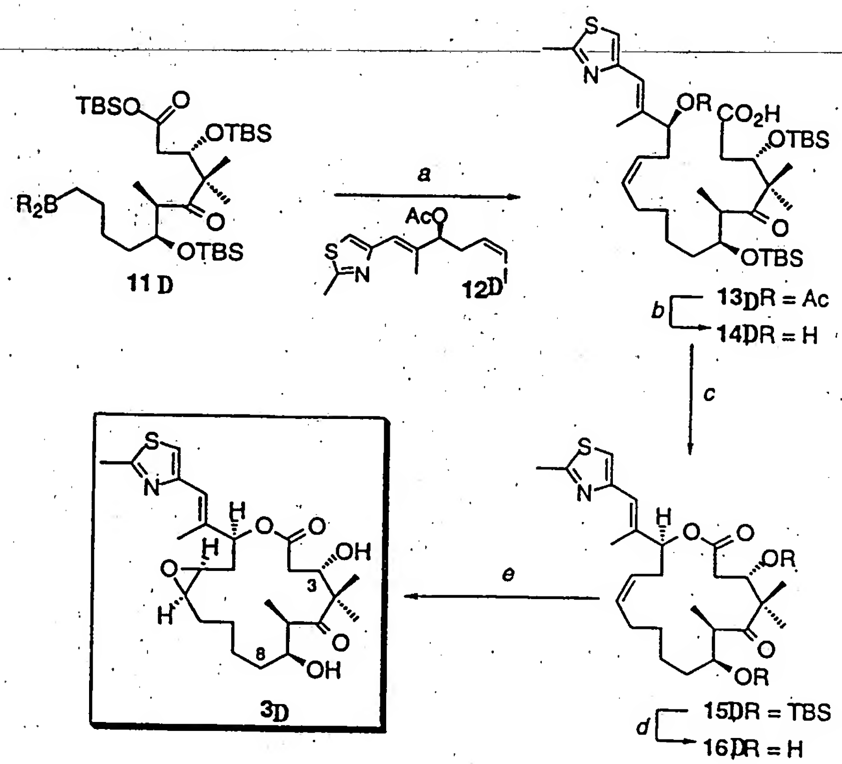


R^1 = H, R^2 = Me; epothilone A
R^1 = R^2 = Me; epothilone B
R^1 = R^2 = H; C_8-desmethyl-epothilone A (3D)



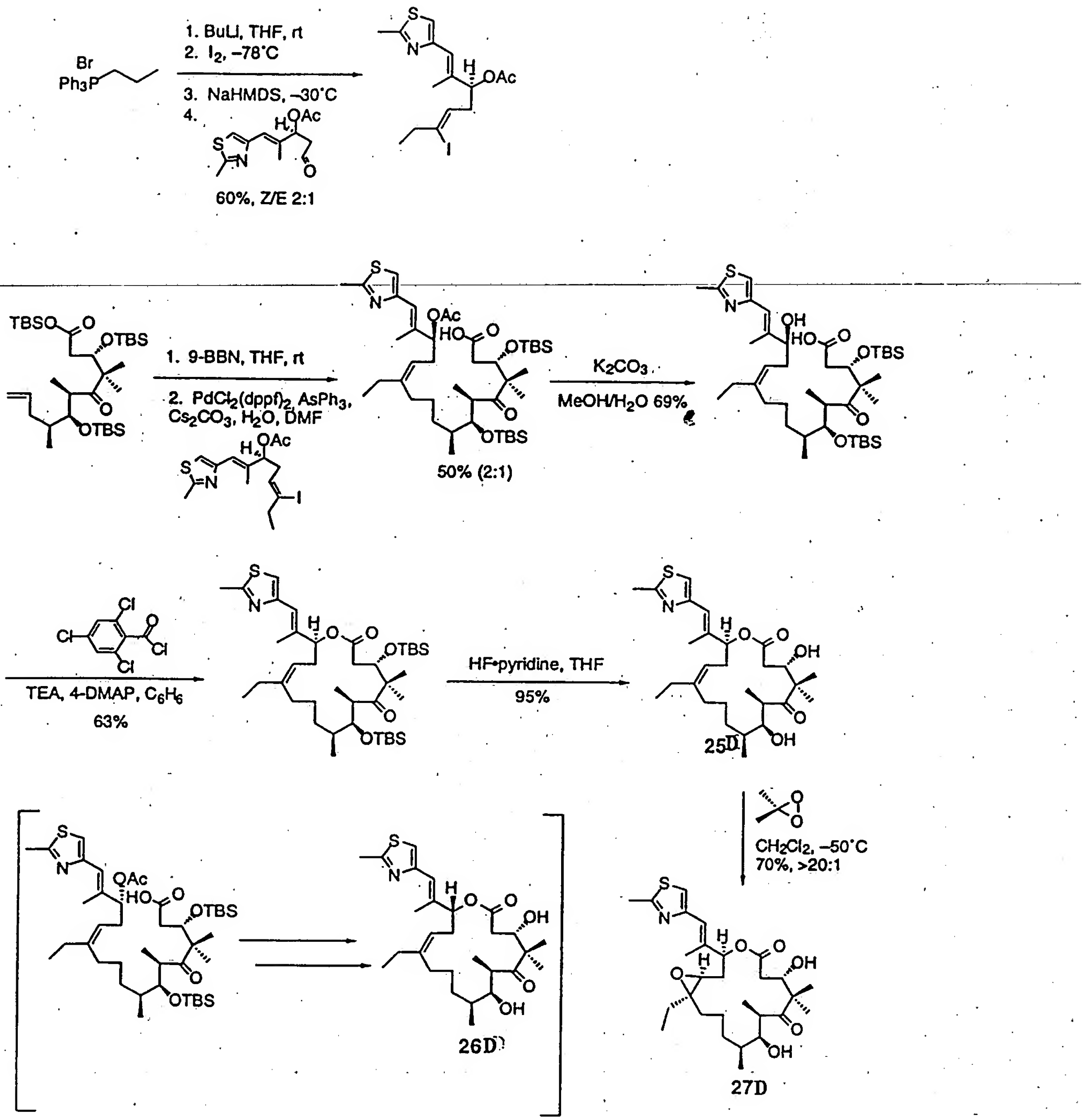
a,b
c
d
e,f
g,h,i,j
k
4 D
5 D
6 D
7 D
8 D
TBS = Si t-buMe2
9DR = t-butyl
10DR = TBS

FIGURE 20



TBSO
O
OTBS
R2B
O
OTBS
11 D
a
AcO
S
N
12D
S
N
OR
CO2H
OTBS
O
OTBS
13DR = Ac
b
14DR = H
c
S
N
H
O
O
OR
O
OR
15DR = TBS
d
16DR = H
e
S
N
H
O
O
OH
H
O
H
3
8
O
OH
3D

FIGURE 21



1. BuLi, THF, rt
2. I2, -78°C
3. NaHMDS, -30°C
4.
60%, Z/E 2:1
1. 9-BBN, THF, rt
2. PdCl2(dppf)2, AsPh3, Cs2CO3, H2O, DMF
50% (2:1)
K2CO3
MeOH/H2O 69%
TEA, 4-DMAP, C6H6
63%
HF•pyridine, THF
95%
25D
CH2Cl2, -50°C
70%, >20:1
26D
27D

FIGURE 22

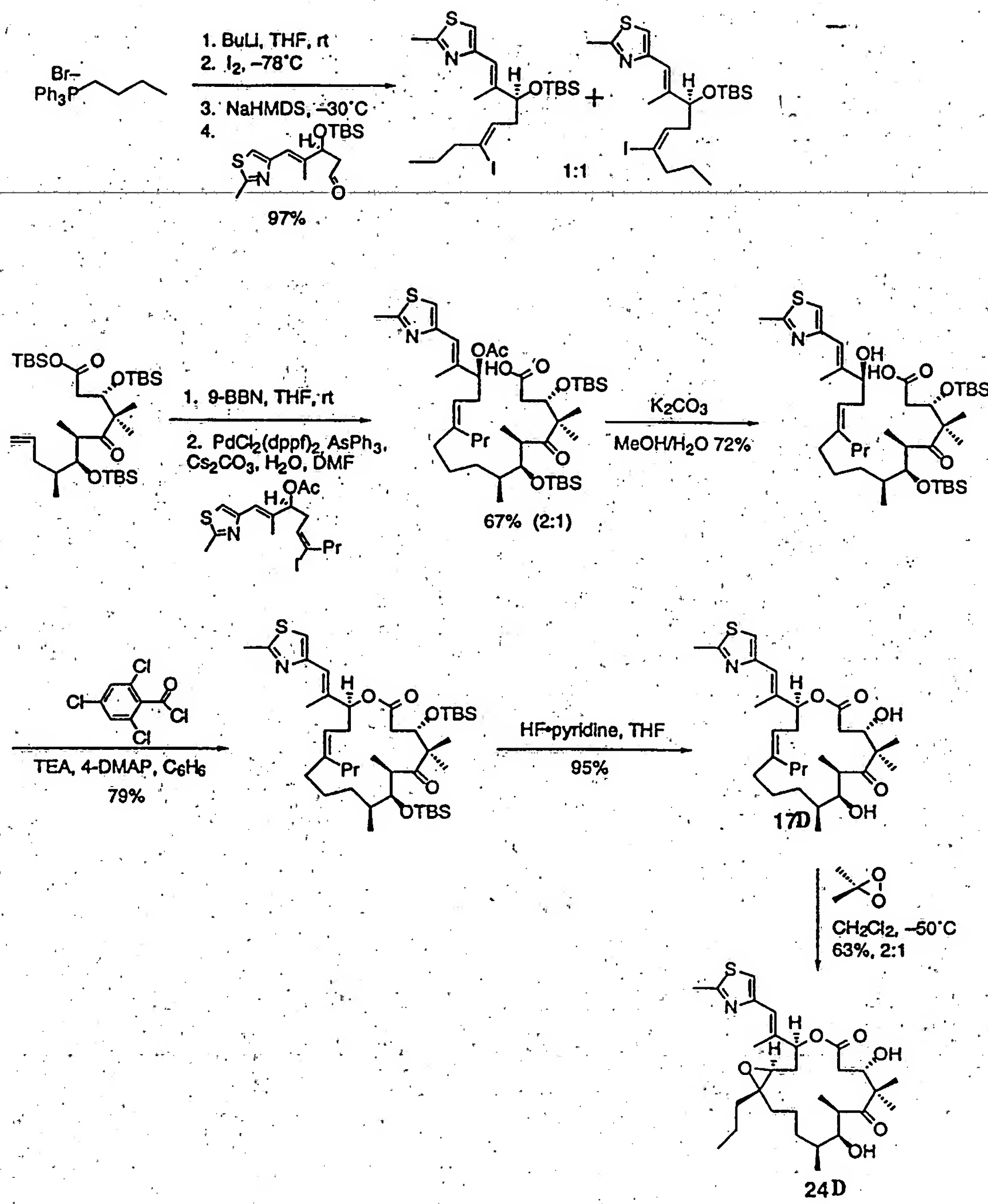
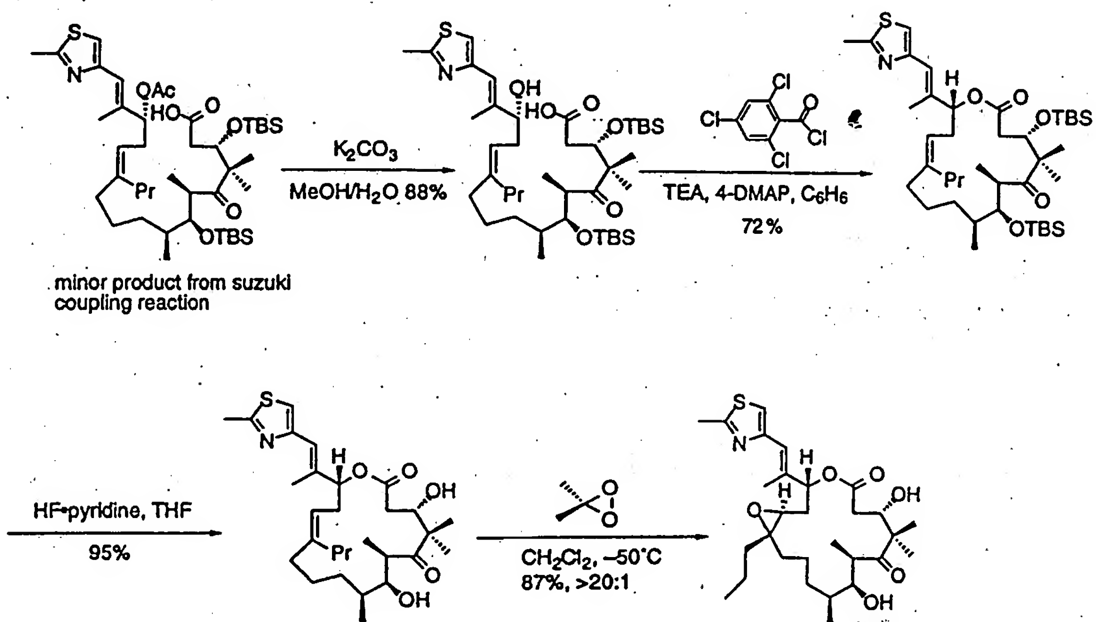

1. BuLi, THF, rt
2. I_2, –78°C
3. NaHMDS, –30°C
4.
97%
1:1
1. 9-BBN, THF, rt
2. $PdCl_2(dppf)_2$, $AsPh_3$, Cs_2CO_3, H_2O, DMF
67% (2:1)
K_2CO_3
$MeOH/H_2O$ 72%
TEA, 4-DMAP, C_6H_6
79%
HF•pyridine, THF
95%
17D
CH_2Cl_2, –50°C
63%, 2:1
24D

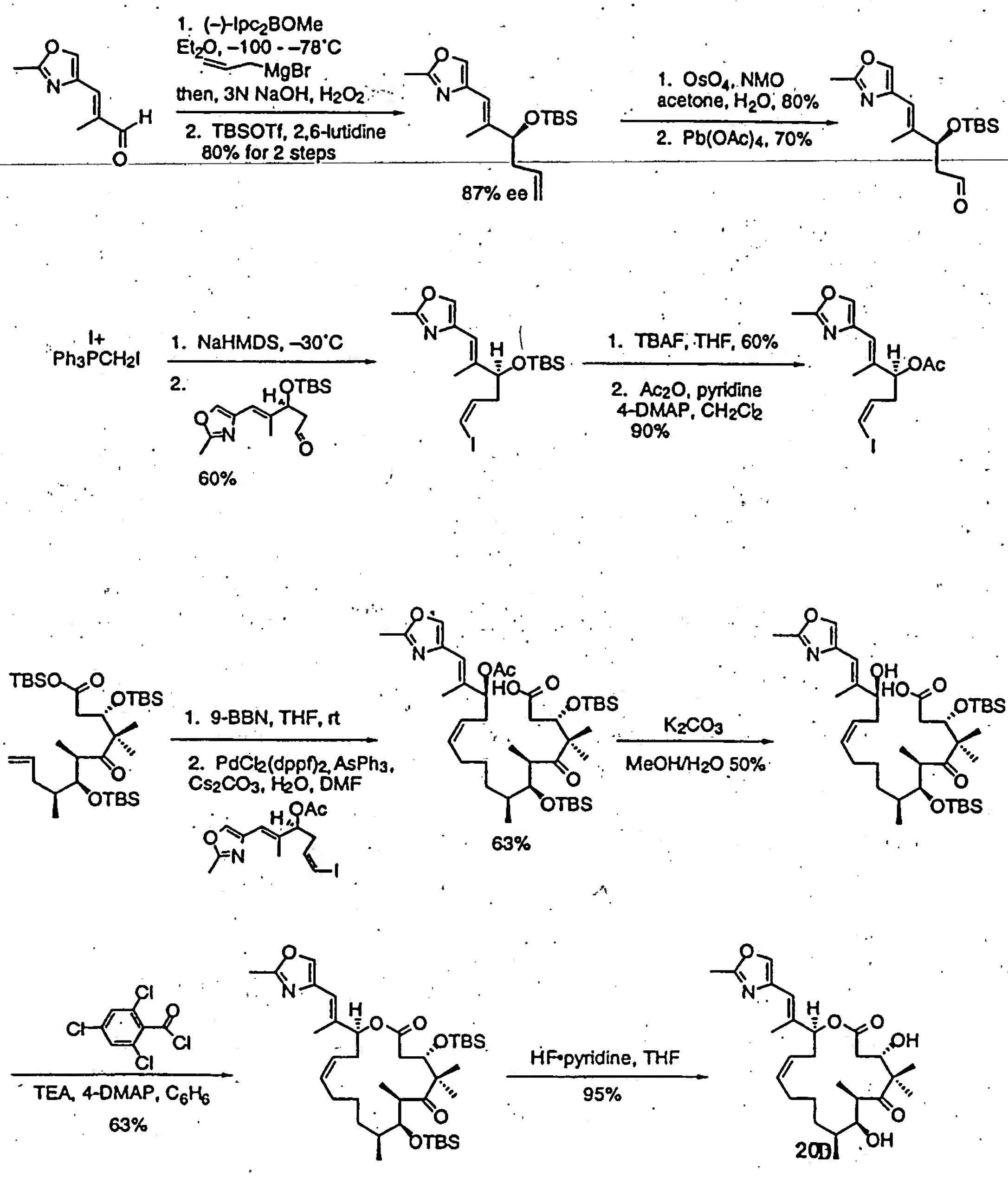
FIGURE 23



18D

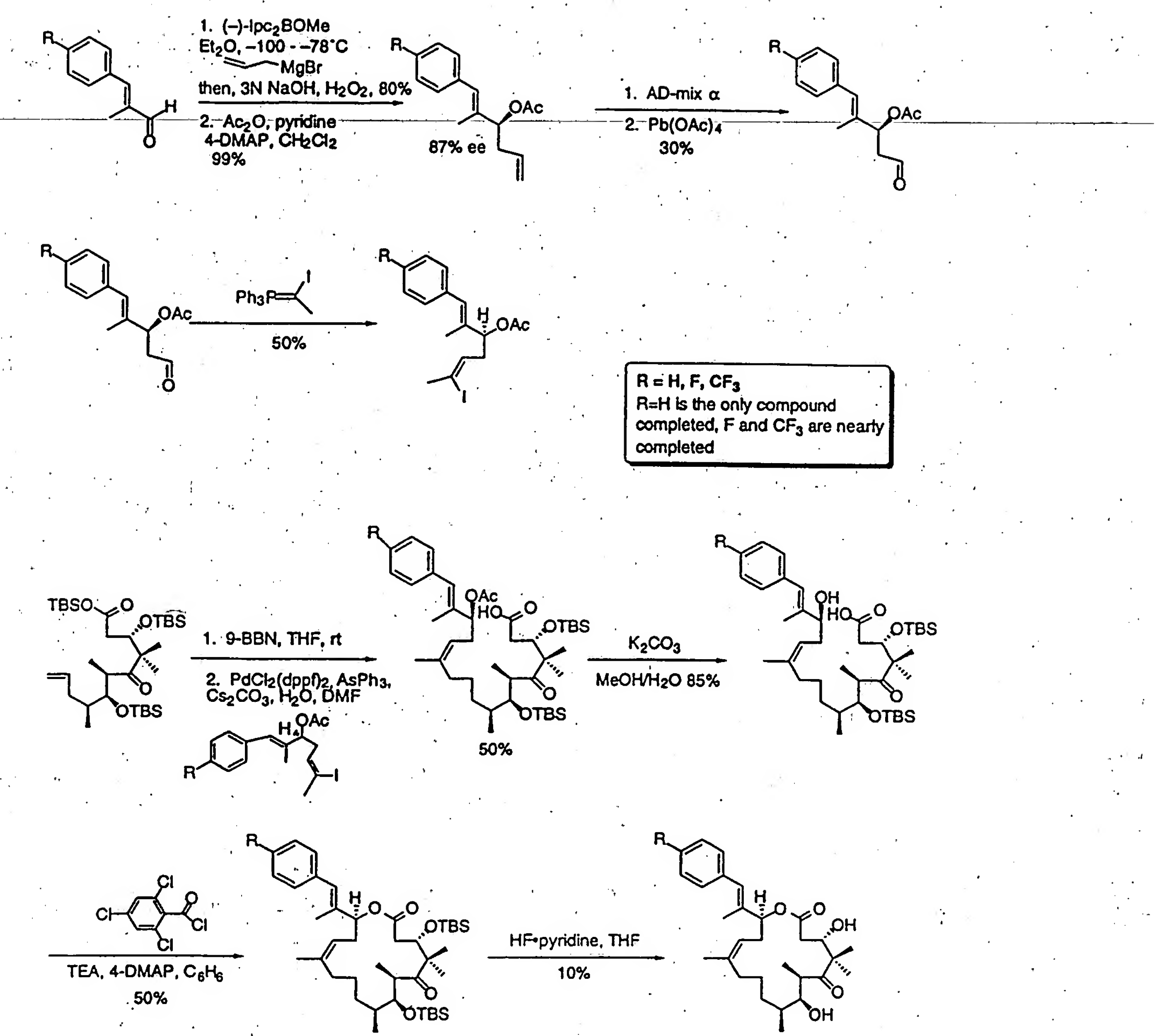
19D

FIGURE 24



1. (–)-Ipc2BOMe
Et2O, –100 - –78°C
MgBr
then, 3N NaOH, H2O2
2. TBSOTf, 2,6-lutidine
80% for 2 steps
OTBS
87% ee
1. OsO4, NMO
acetone, H2O, 80%
2. Pb(OAc)4, 70%
OTBS
I+
Ph3PCH2I
1. NaHMDS, –30°C
2.
OTBS
60%
OTBS
1. TBAF, THF, 60%
2. Ac2O, pyridine
4-DMAP, CH2Cl2
90%
OAc
TBSO
OTBS
OTBS
1. 9-BBN, THF, rt
2. PdCl2(dppf)2, AsPh3,
Cs2CO3, H2O, DMF
OAc
OAc
HO
OTBS
OTBS
63%
K2CO3
MeOH/H2O 50%
OH
HO
OTBS
OTBS
TEA, 4-DMAP, C6H6
63%
OTBS
OTBS
HF•pyridine, THF
95%
OH
OH
20D

FIGURE 25



22D (R = H)

FIGURE 26

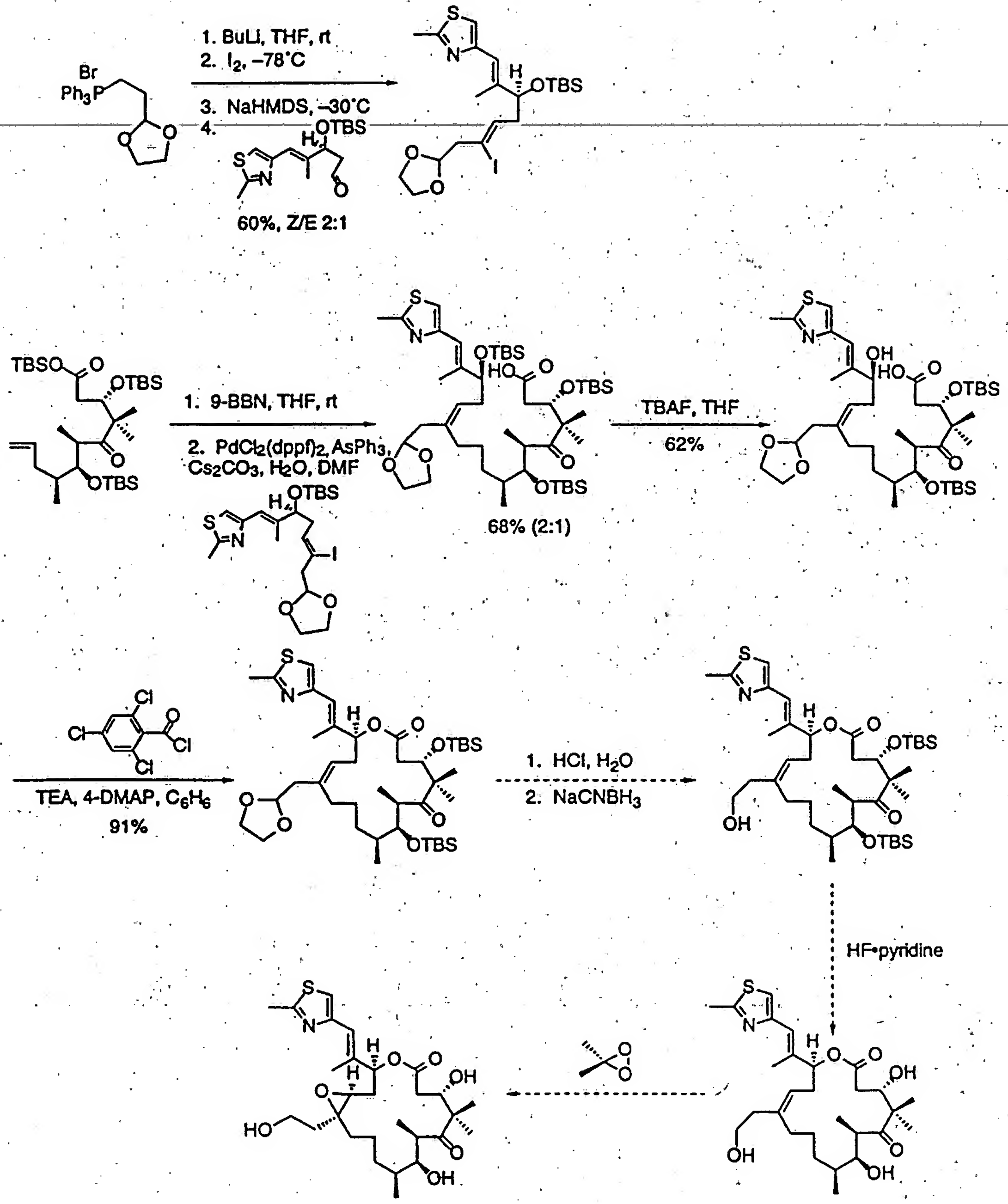

1. BuLi, THF, rt
2. I_2, -78°C
3. NaHMDS, -30°C
4.
60%, Z/E 2:1
1. 9-BBN, THF, rt
2. $PdCl_2(dppf)_2$, $AsPh_3$, Cs_2CO_3, H_2O, DMF
68% (2:1)
TBAF, THF
62%
TEA, 4-DMAP, C_6H_6
91%
1. HCl, H_2O
2. $NaCNBH_3$
HF•pyridine

FIGURE 27

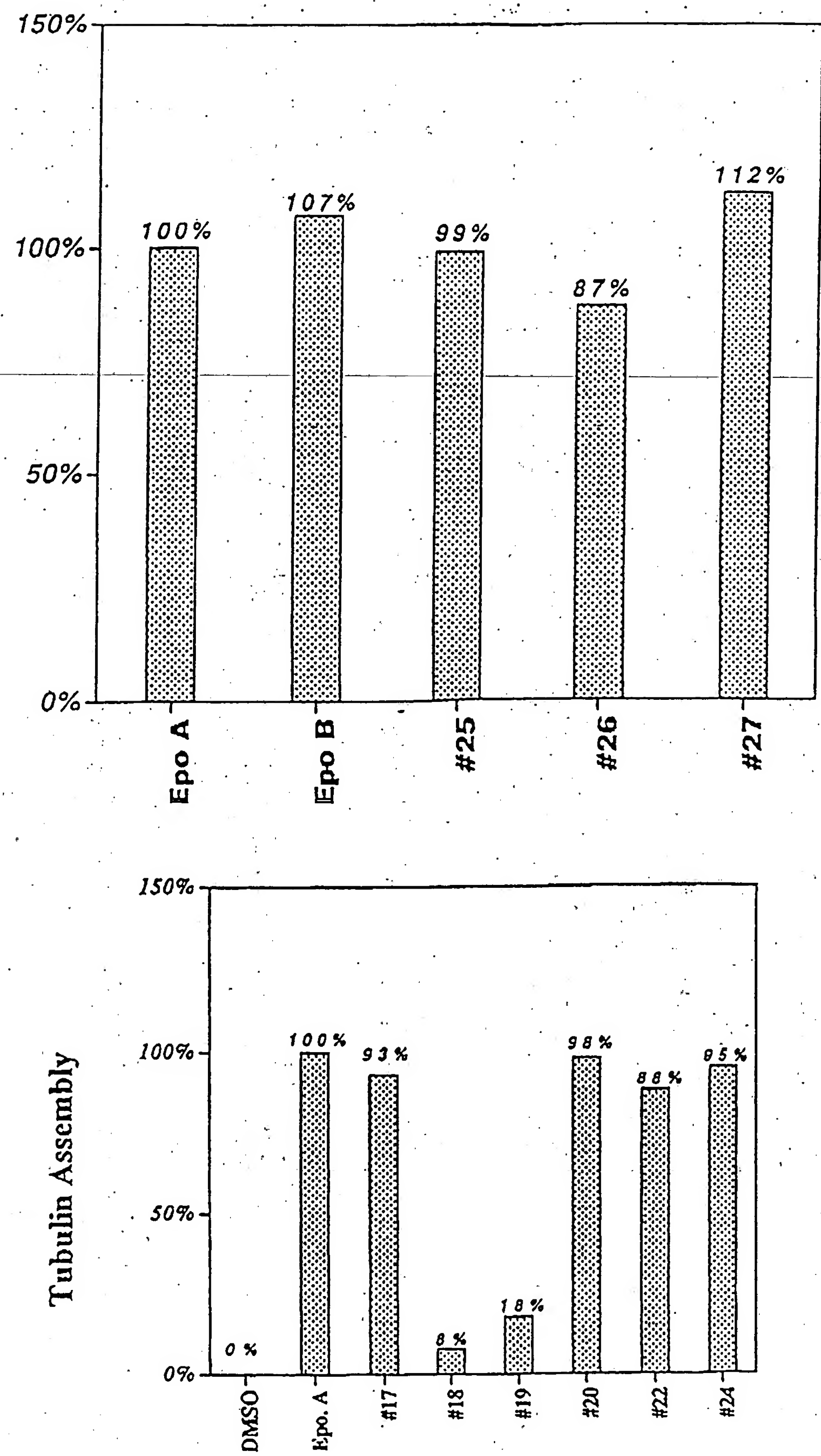

150%
100%
50%
0%
100%
107%
99%
87%
112%
Epo A
Epo B
#25
#26
#27
Tubulin Assembly
150%
100%
50%
0%
0 %
100 %
93 %
8 %
18 %
98 %
88 %
95 %
DMSO
Epo. A
#17
#18
#19
#20
#22
#24

FIGURE 28

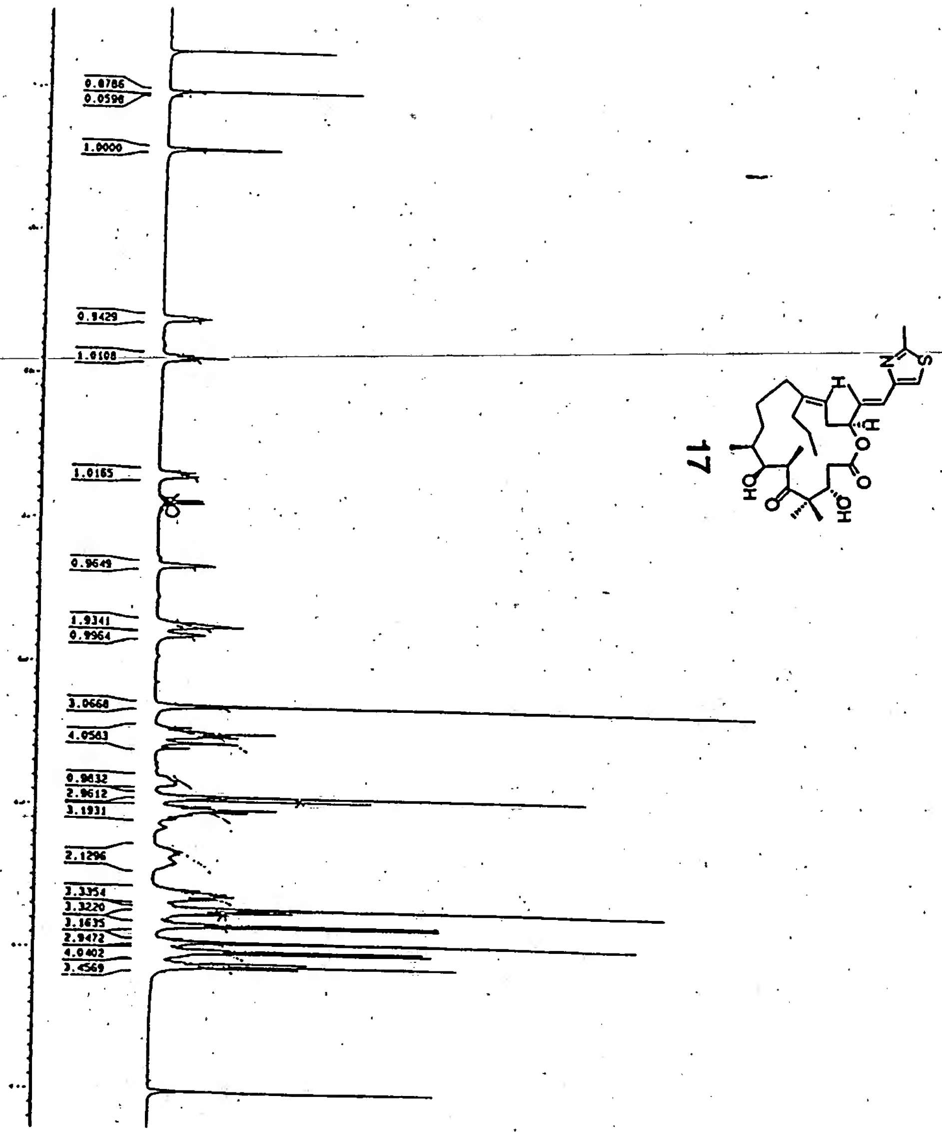
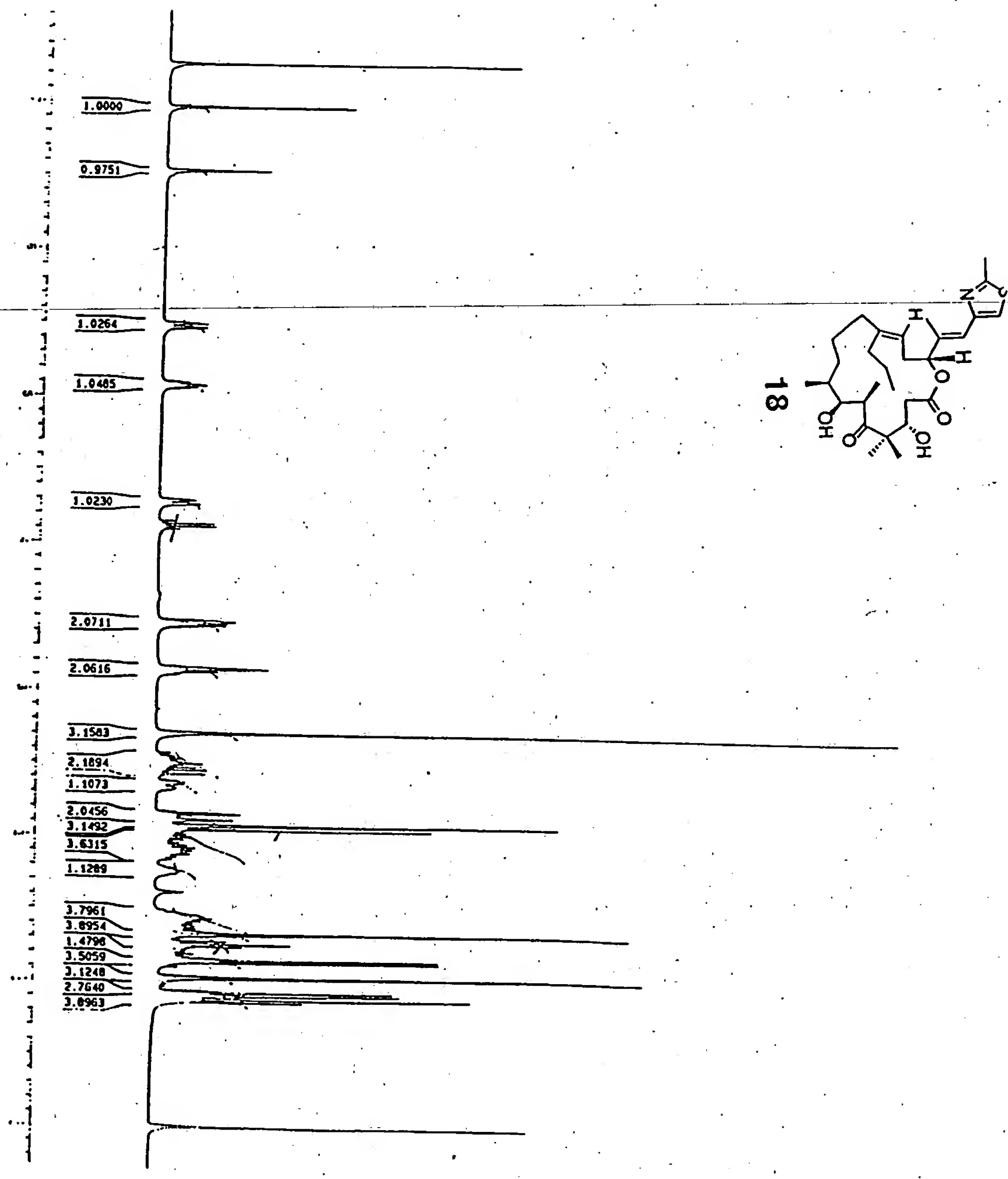

0.0786
0.0598
1.0000
0.9429
1.0108
1.0165
0.9649
1.9341
0.9964
3.0668
4.0563
0.9832
2.9612
3.1931
2.1296
3.3354
3.3220
3.1635
2.9472
4.0402
3.4569
17

FIGURE 29



18

FIGURE 30

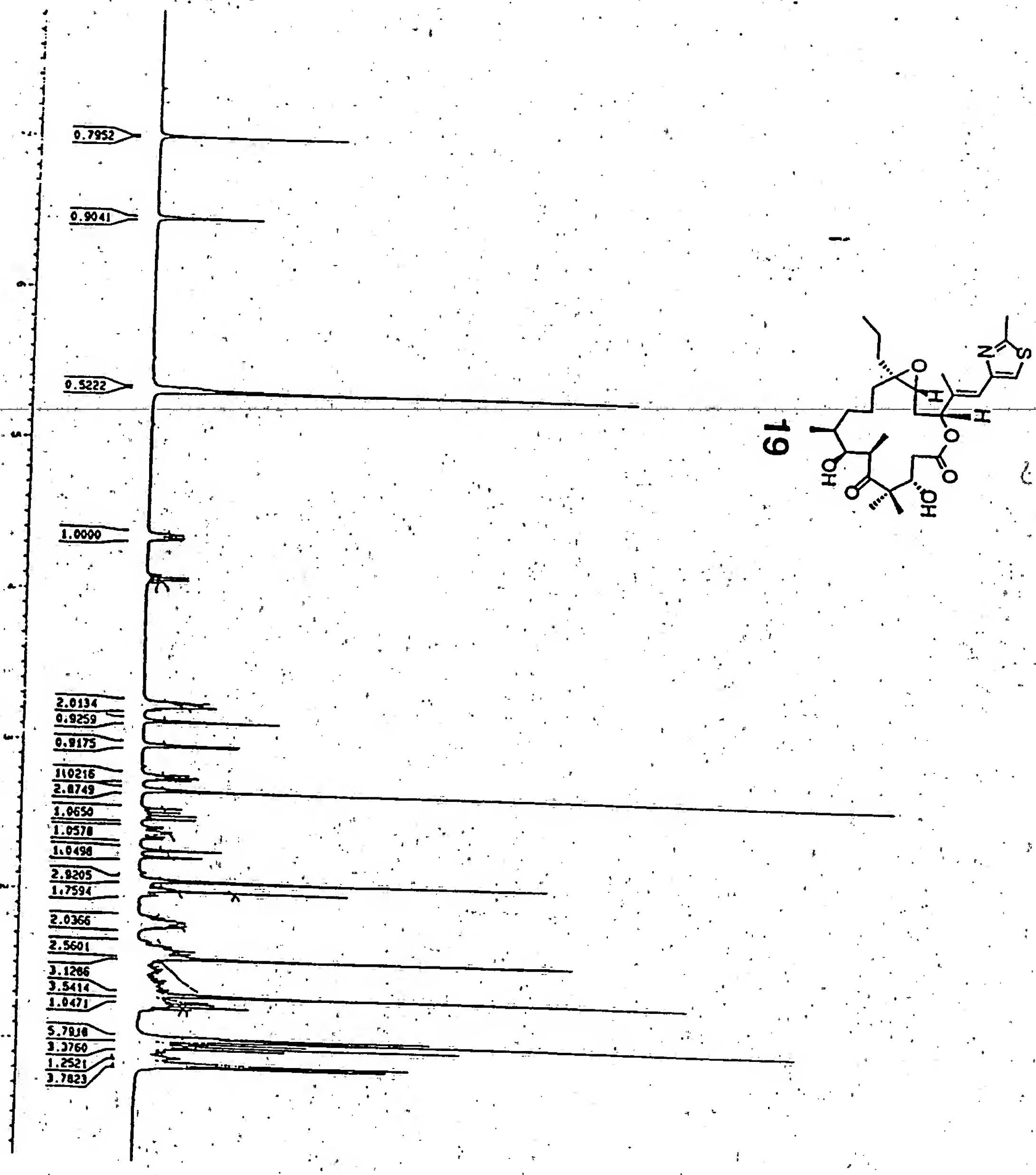


FIGURE 31

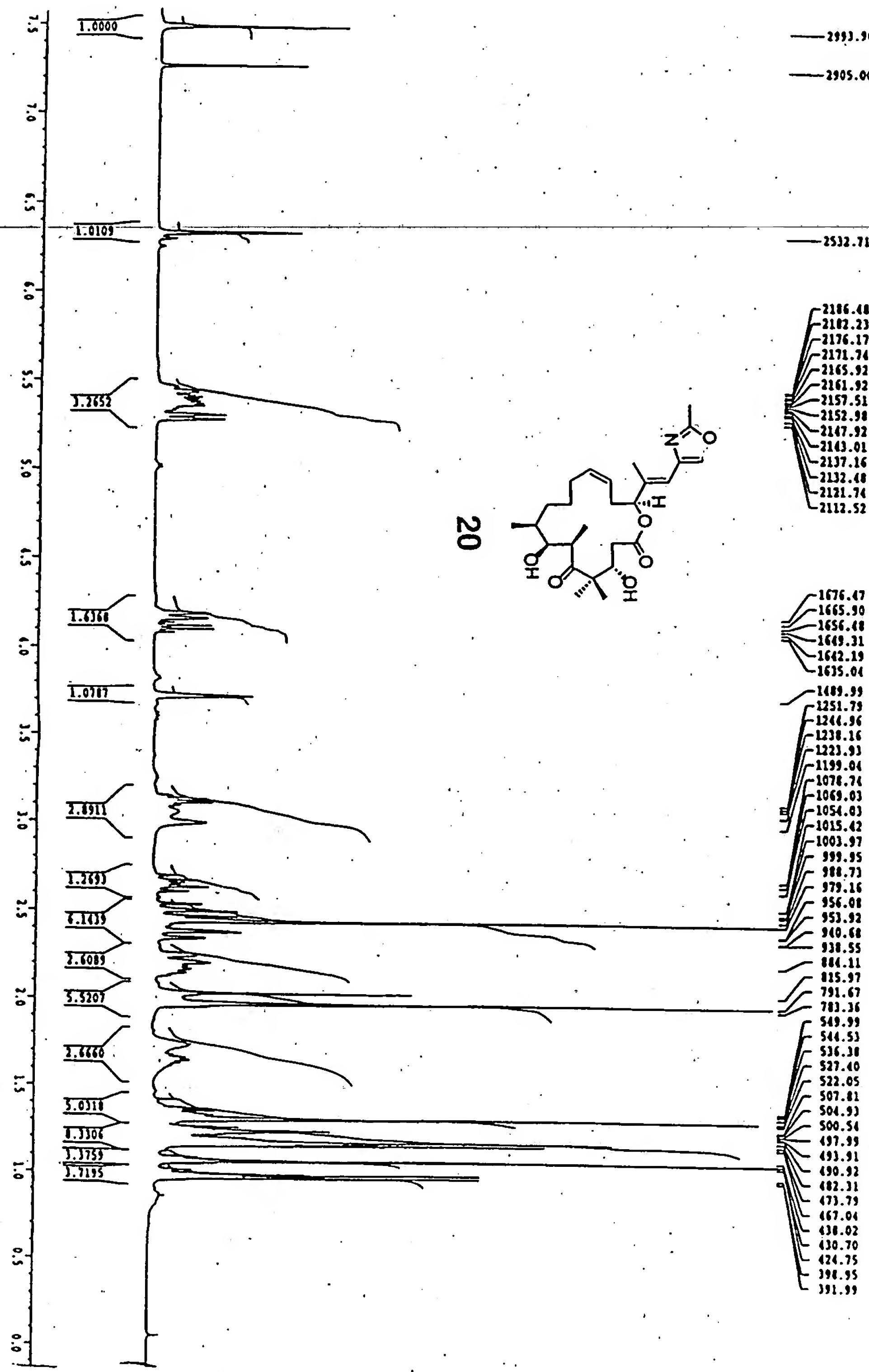


FIGURE 32

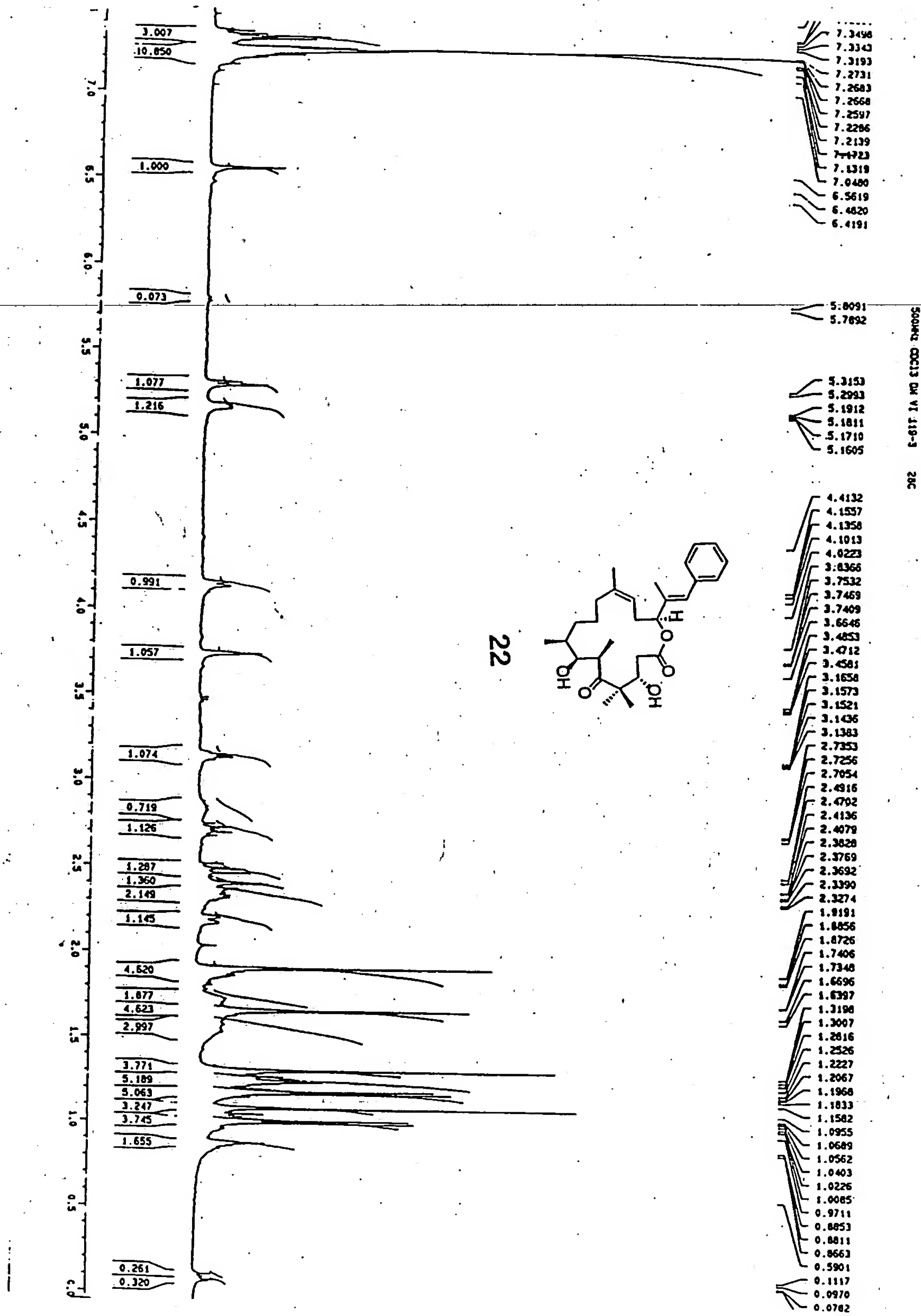


FIGURE 33

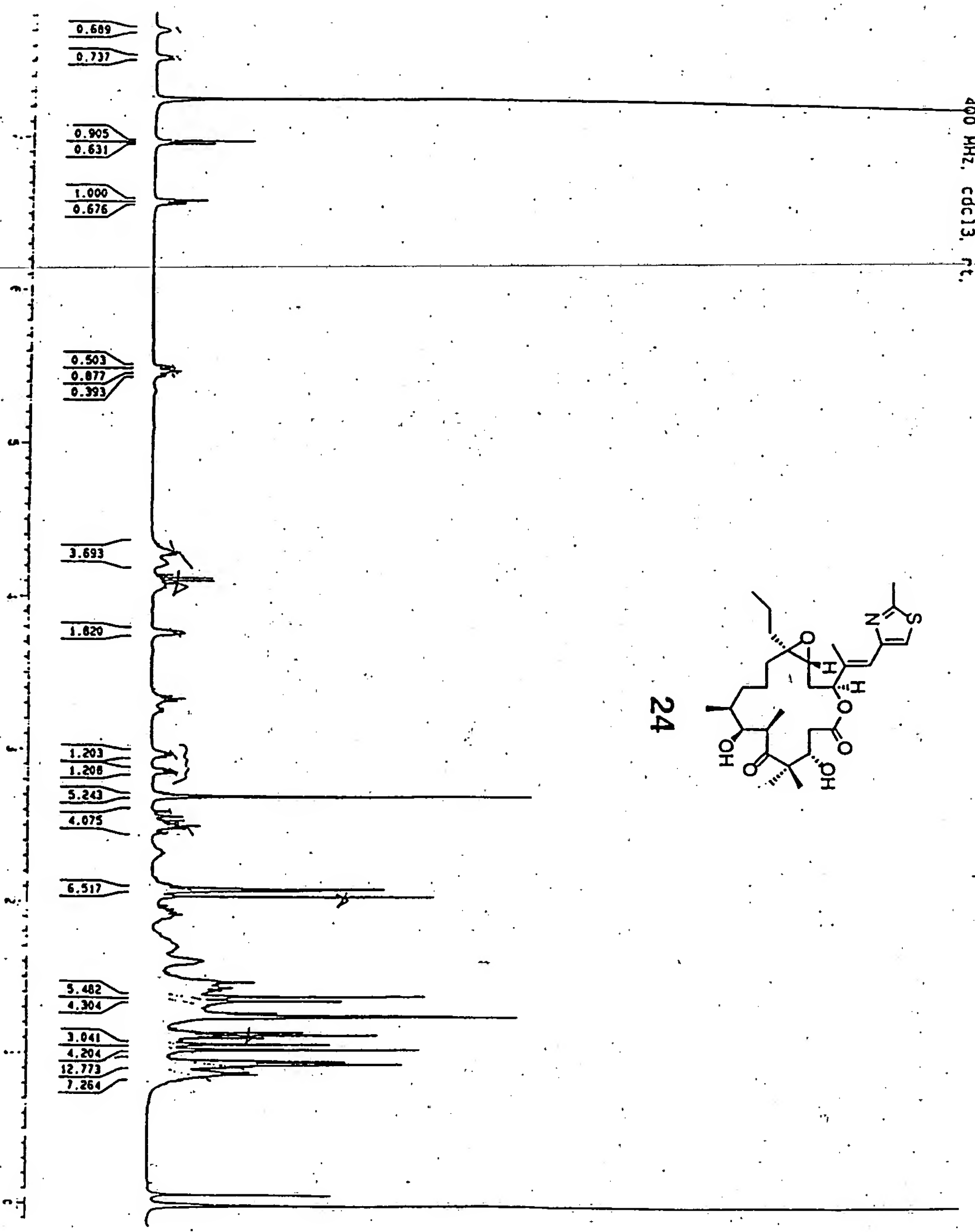


FIGURE 34

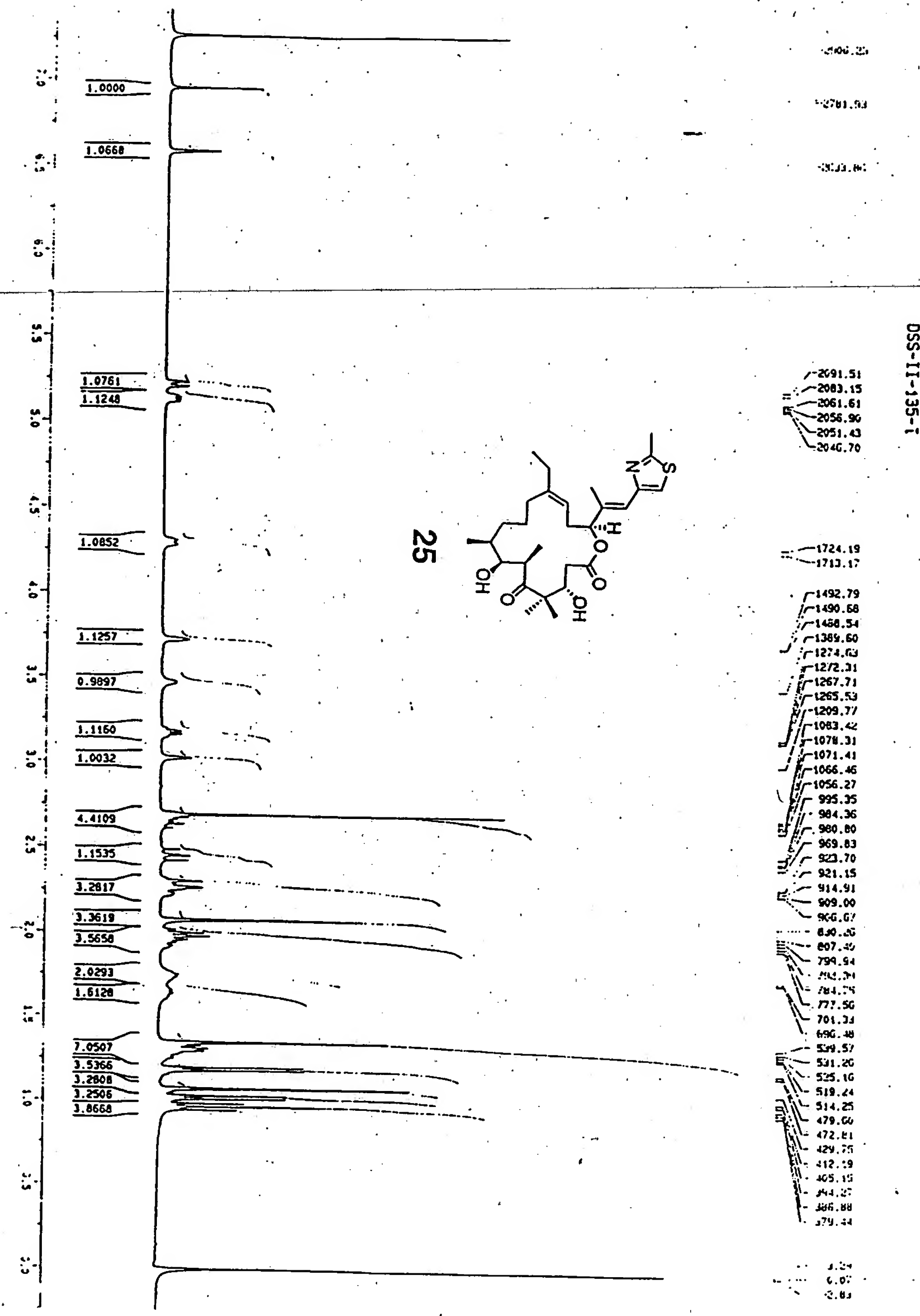


FIGURE 35

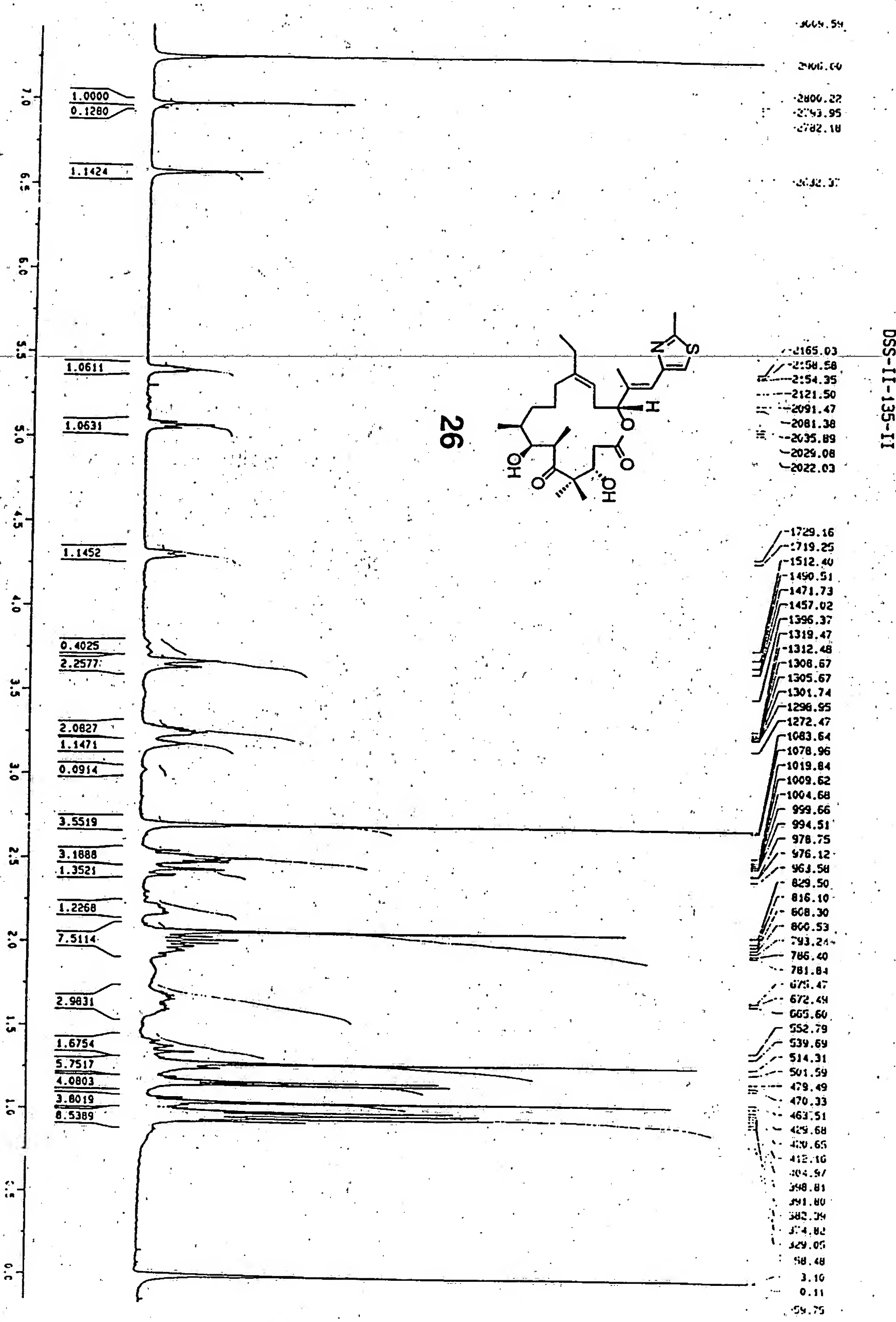


FIGURE 36

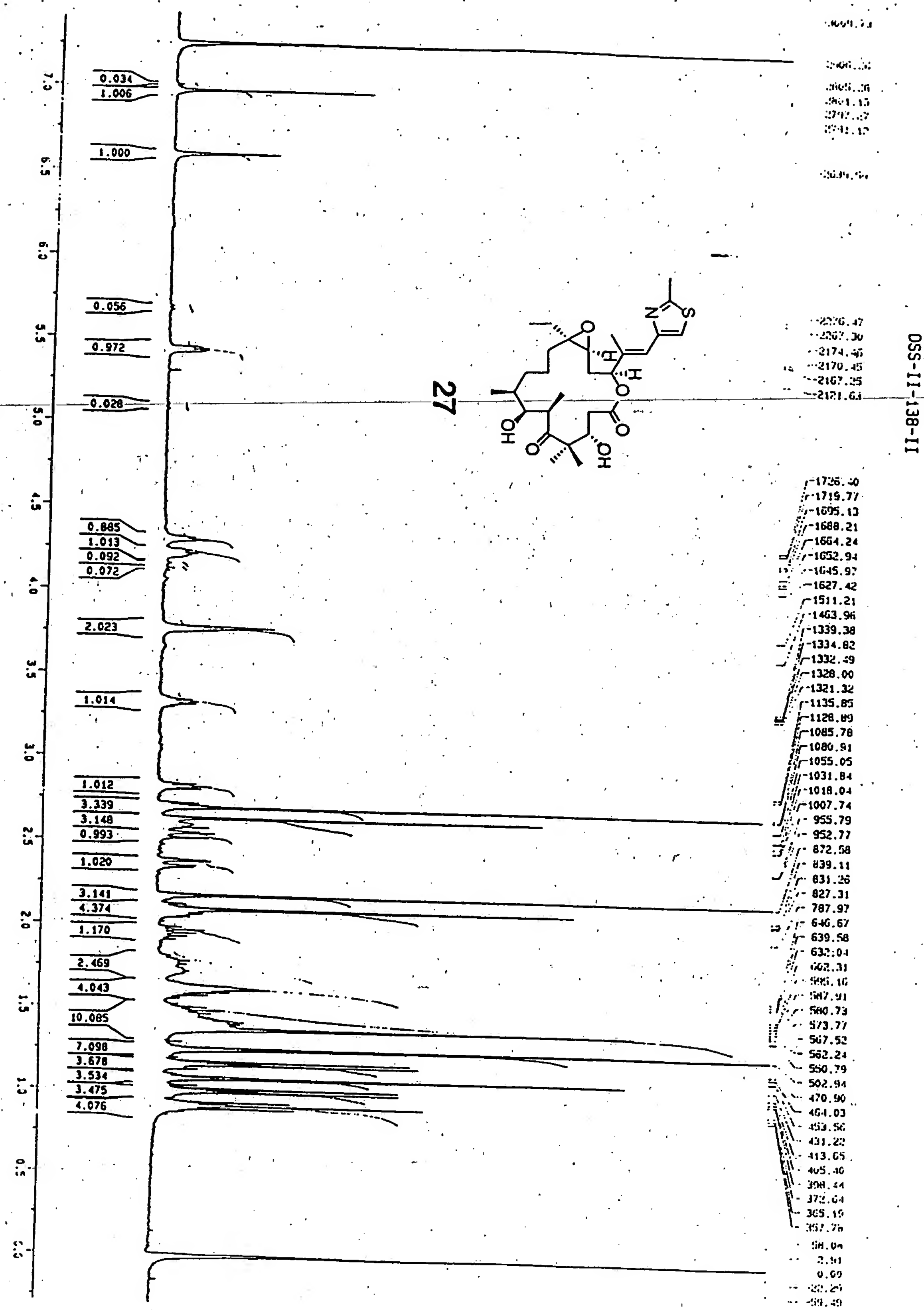


FIGURE 37

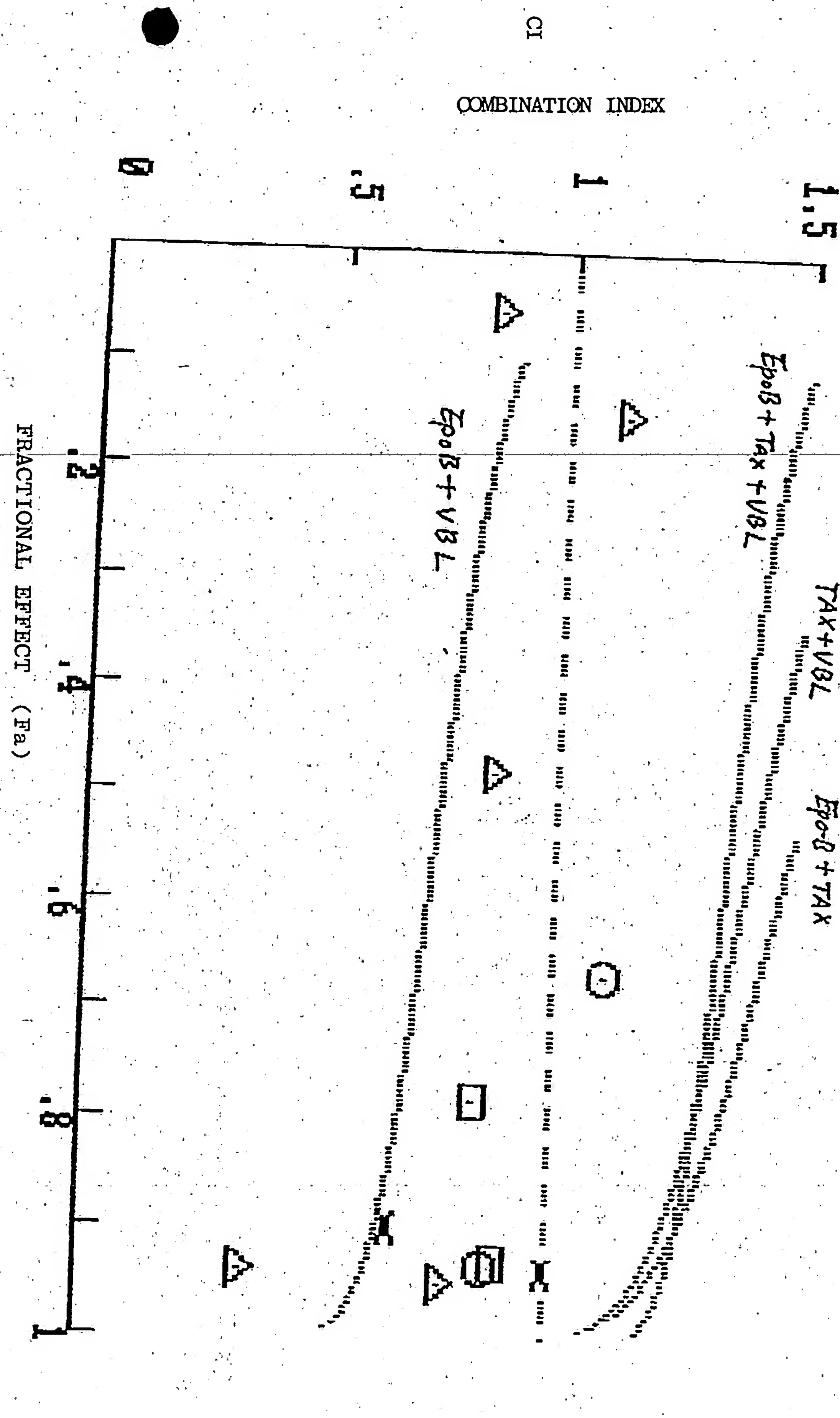
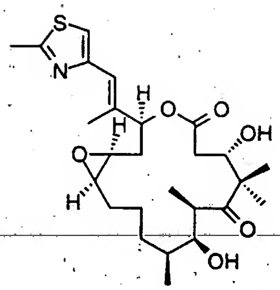
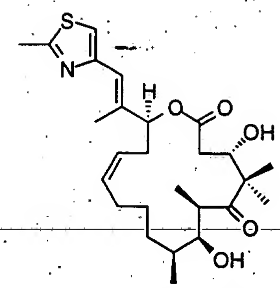

CI
COMBINATION INDEX
0
.5
1
1.5
FRACTIONAL EFFECT (Fa)
.2
.4
.6
.8
1
EpoB + Tax + VBL
TAX+VBL
Epo-B + TAX
EpoB + VBL

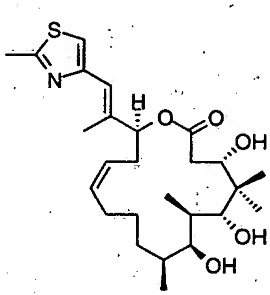
Figure 38



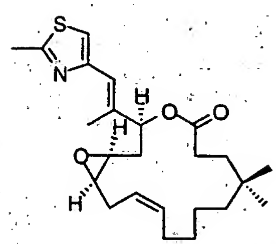
epothilone A
(0.0027)
[0.020]



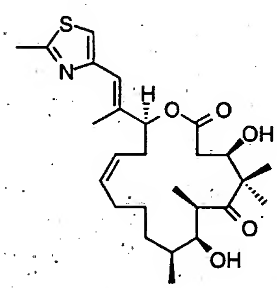
desoxyepothilone A
1
(0.022)
[0.012]



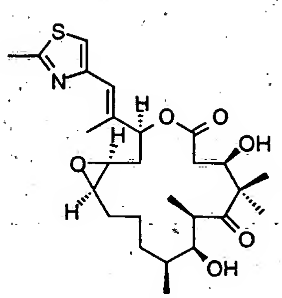
2
(14.23)
[6.28]



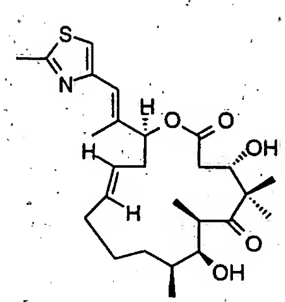
3
(271.1)
[22.4]



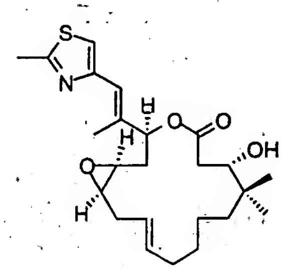
4
(2.12)
[43.0]



5
(>20)
[35.2]

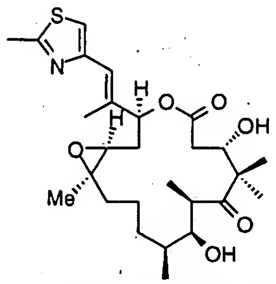


6
(0.052)
[0.035]



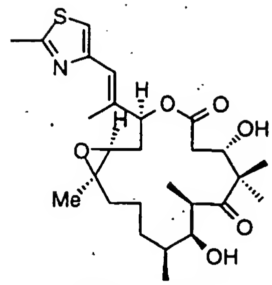
7
(7.36)
[9.82]

Fig. 39



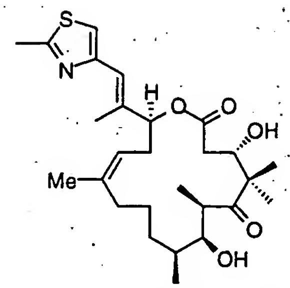
synthetic epothilone B

8
(0.00044)
[0.0026]



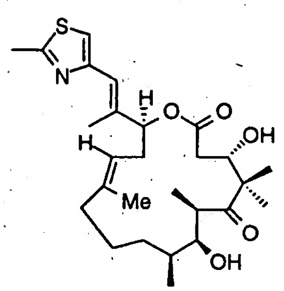
natural epothilone B

9
(0.00017)
[0.0012]

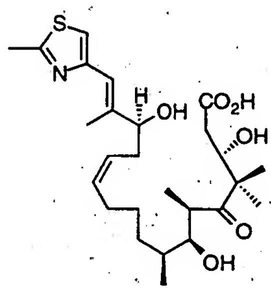


desoxyepothilone B

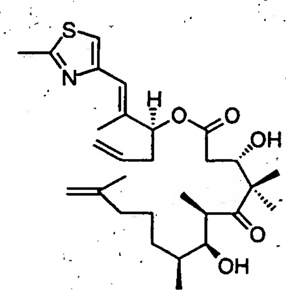
10
(0.0095)
[0.017]



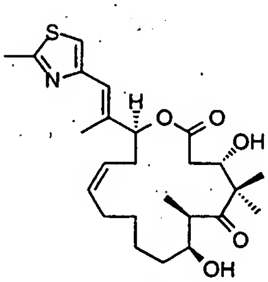
11
(0.090)
[0.262]



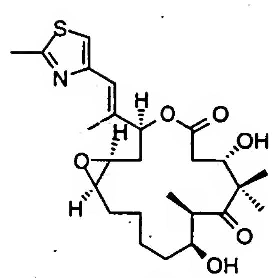
12
(0.79)
[>5]



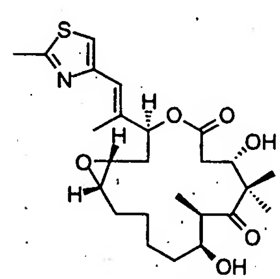
13
(11.53)
[5.63]



14
(5.42)
[5.75]

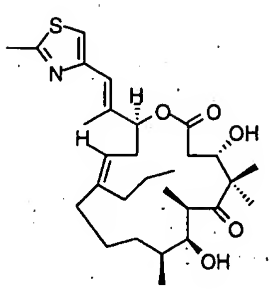


15
(0.96)
[5.95]

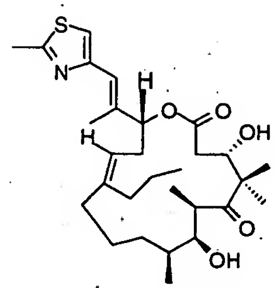


16
(7.47)
[16.48]

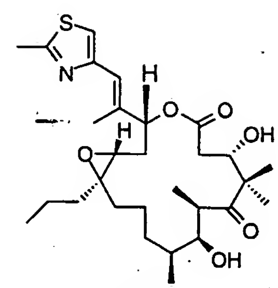
Fig. 40



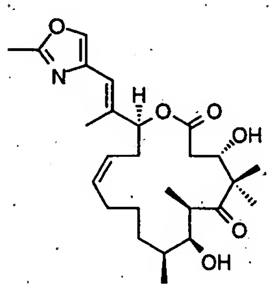
17
(0.090)
[0.254]



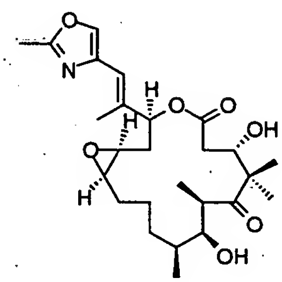
18
(1158)
[>720]



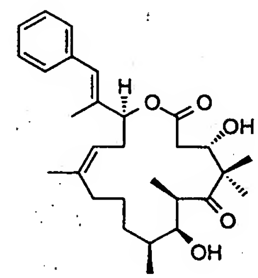
19
(0.96)
[>1.0]



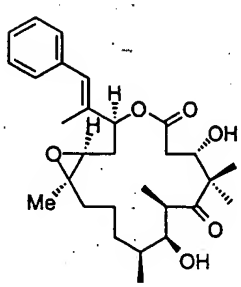
20
(0.030)
[0.049]



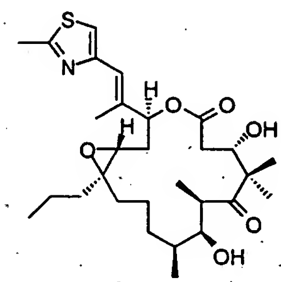
21



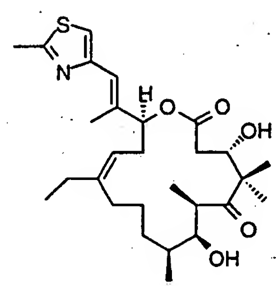
22
(0.098)
[0.146]



23

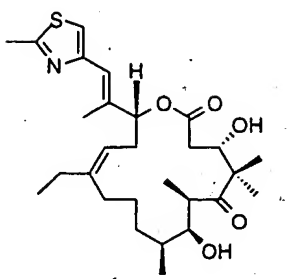


24
(0.0043)
[0.032]

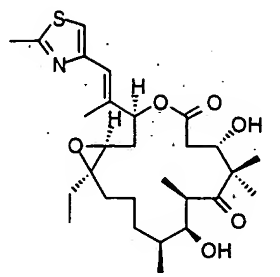


25
(0.021)
[0.077]

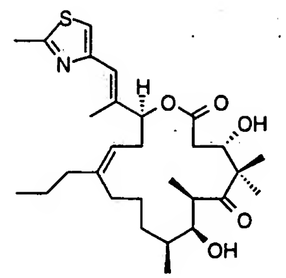
Fig. 41



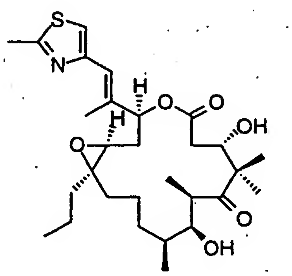
26
(0.055)
[0.197]



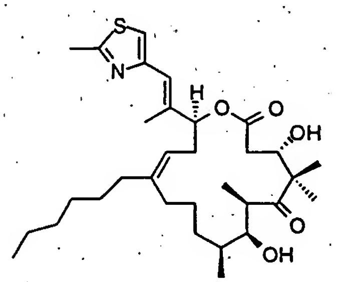
27
(0.0010)
[0.0072]



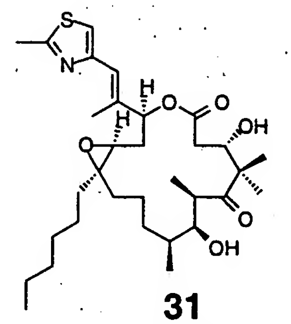
28
(0.039)
[0.067]



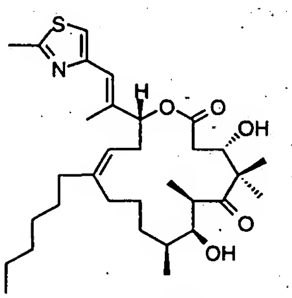
29
(0.0038)
[0.0064]



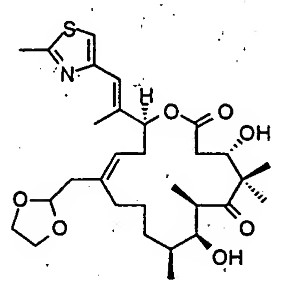
30
(0.044)
[0.108]



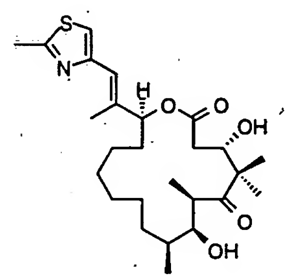
31
(0.027)
[0.049]



32
(0.063)
[0.380]

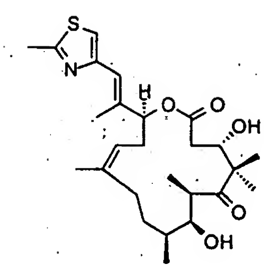


33
(0.0031)
[0.0093]

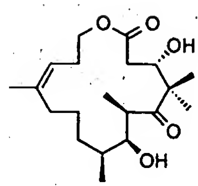


34
(0.143)
[0.276]

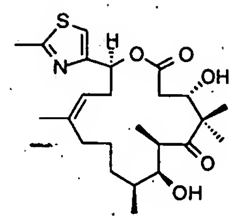
Fig. 42(A)



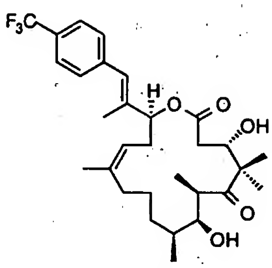
35
(>10)
[8.95]



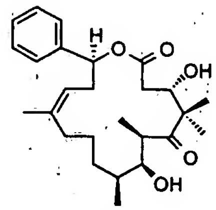
36
(234.5)
[>10]



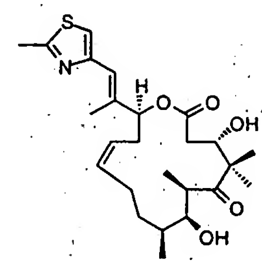
37
(3.25)
[1.20]



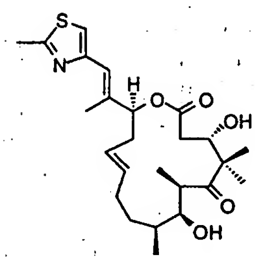
38
(0.254)
[>5.0]



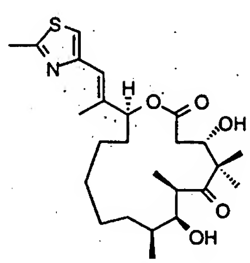
39
(1.80)
[>5.0]



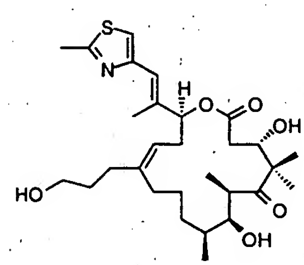
40
(36.9)
[47.3]



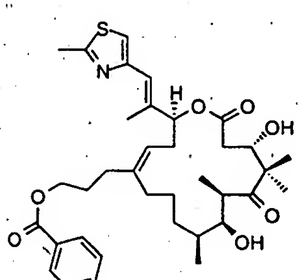
41
(60.1)
[59.2]



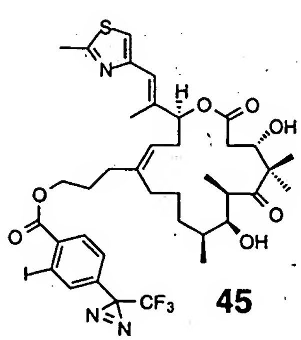
42
(7.41)
[12.9]



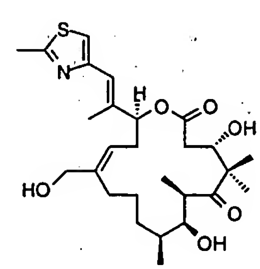
43
(0.0095)
[0.167]



44 (0.250)
[0.905]

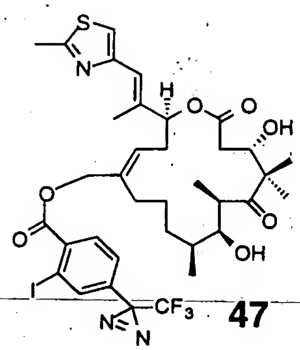


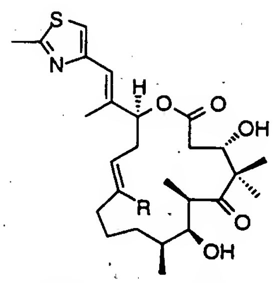
45



46 (0.049)
[>1.0]

Fig. 42(B)


47


48 R = $(CH_2)_3OH$

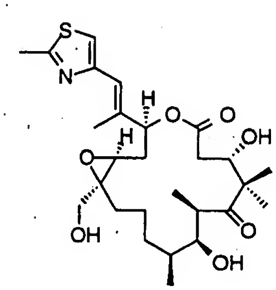
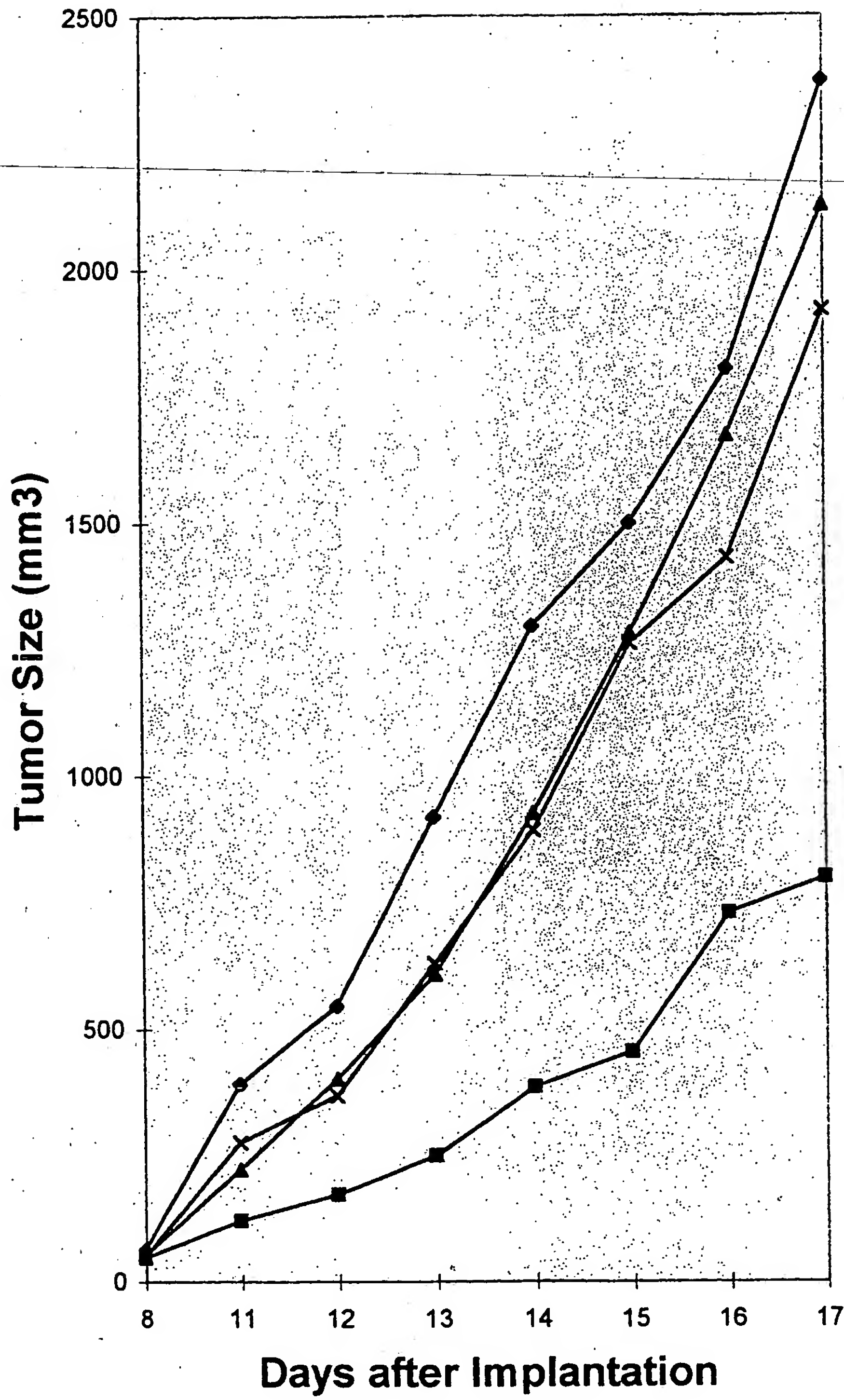

49

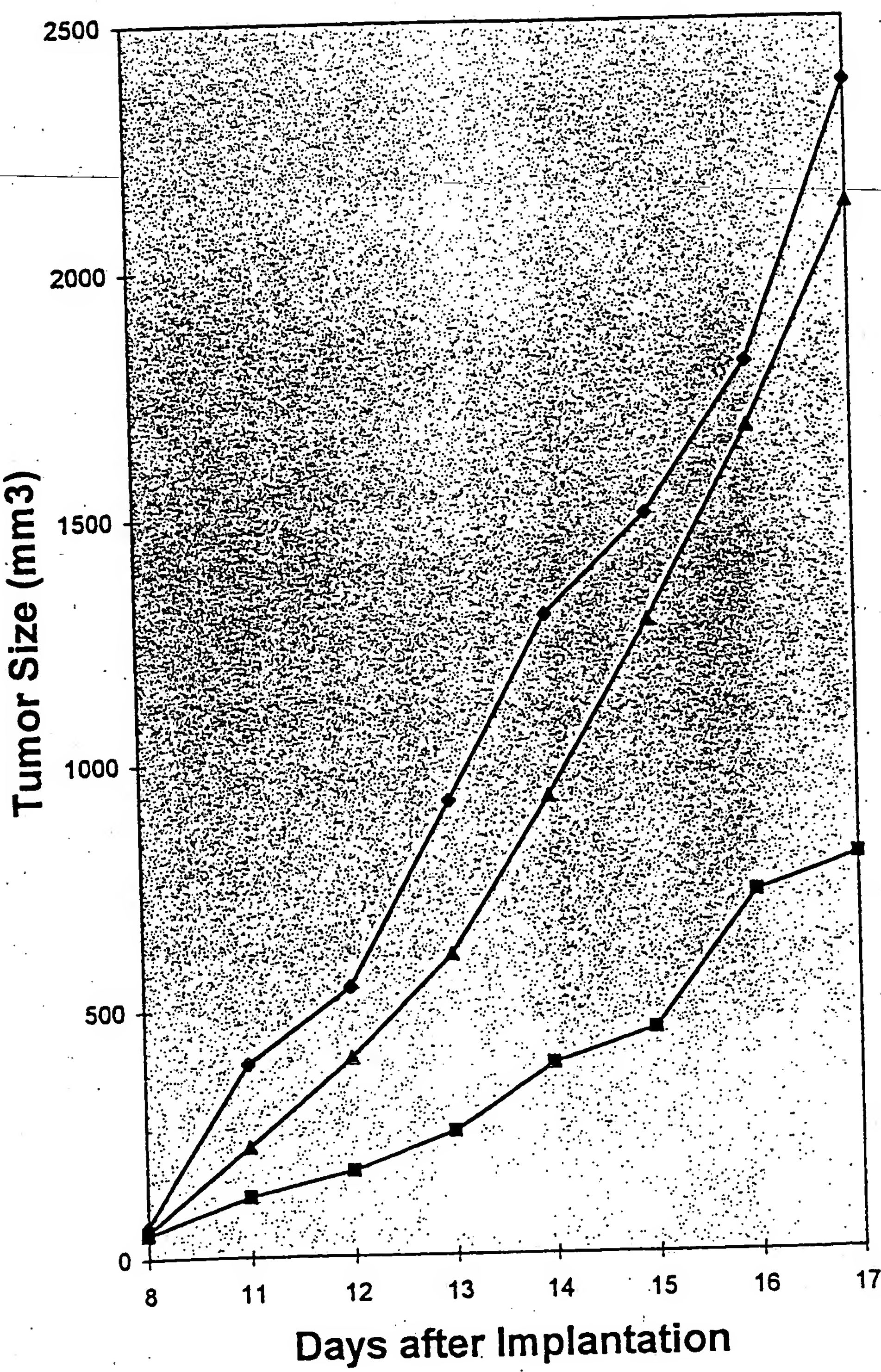
Fig. 42(C)

Fig. 43(A)

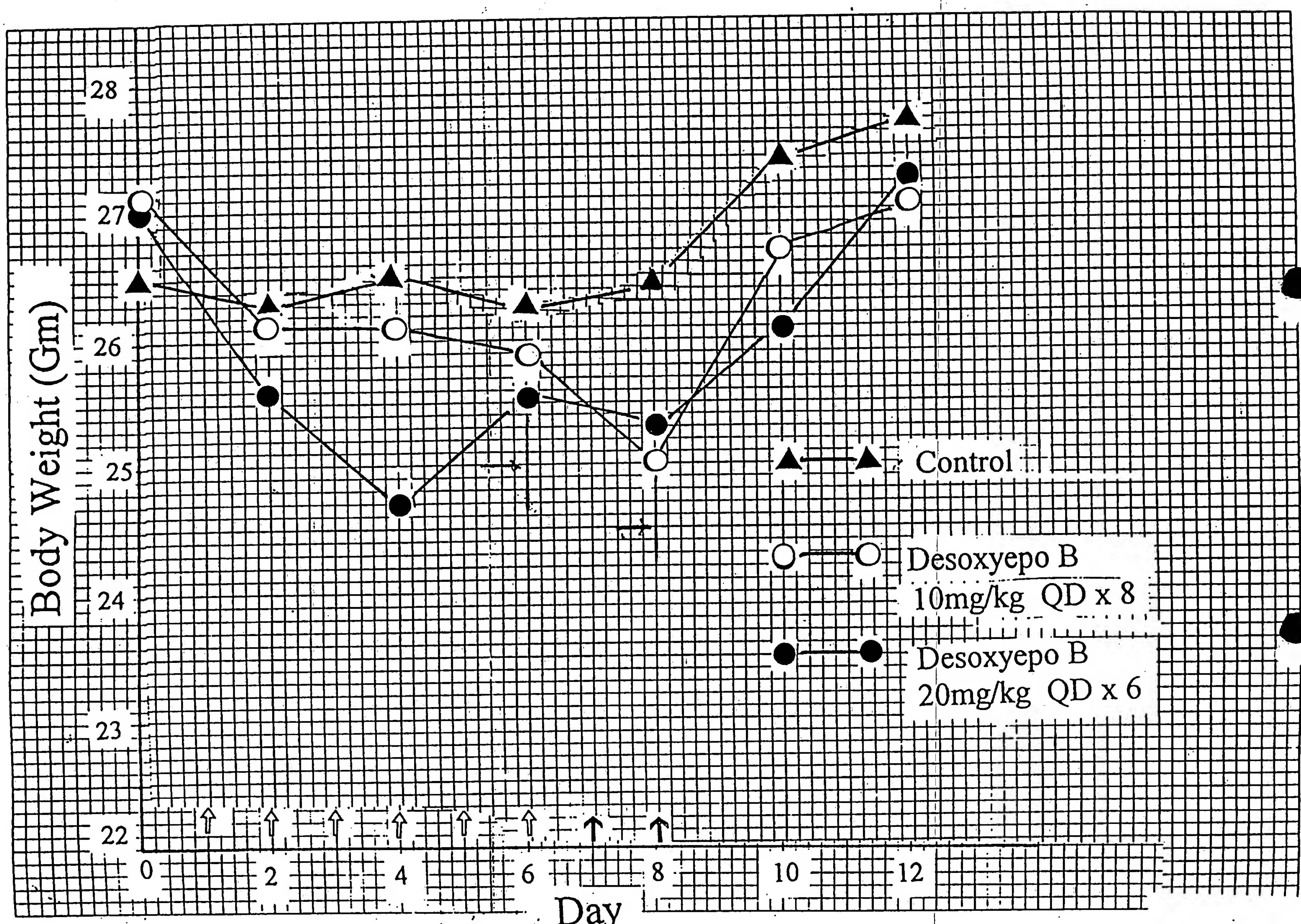


2500
2000
1500
1000
500
0
Tumor Size (mm3)
8
11
12
13
14
15
16
17
Days after Implantation

Fig. 43(B)

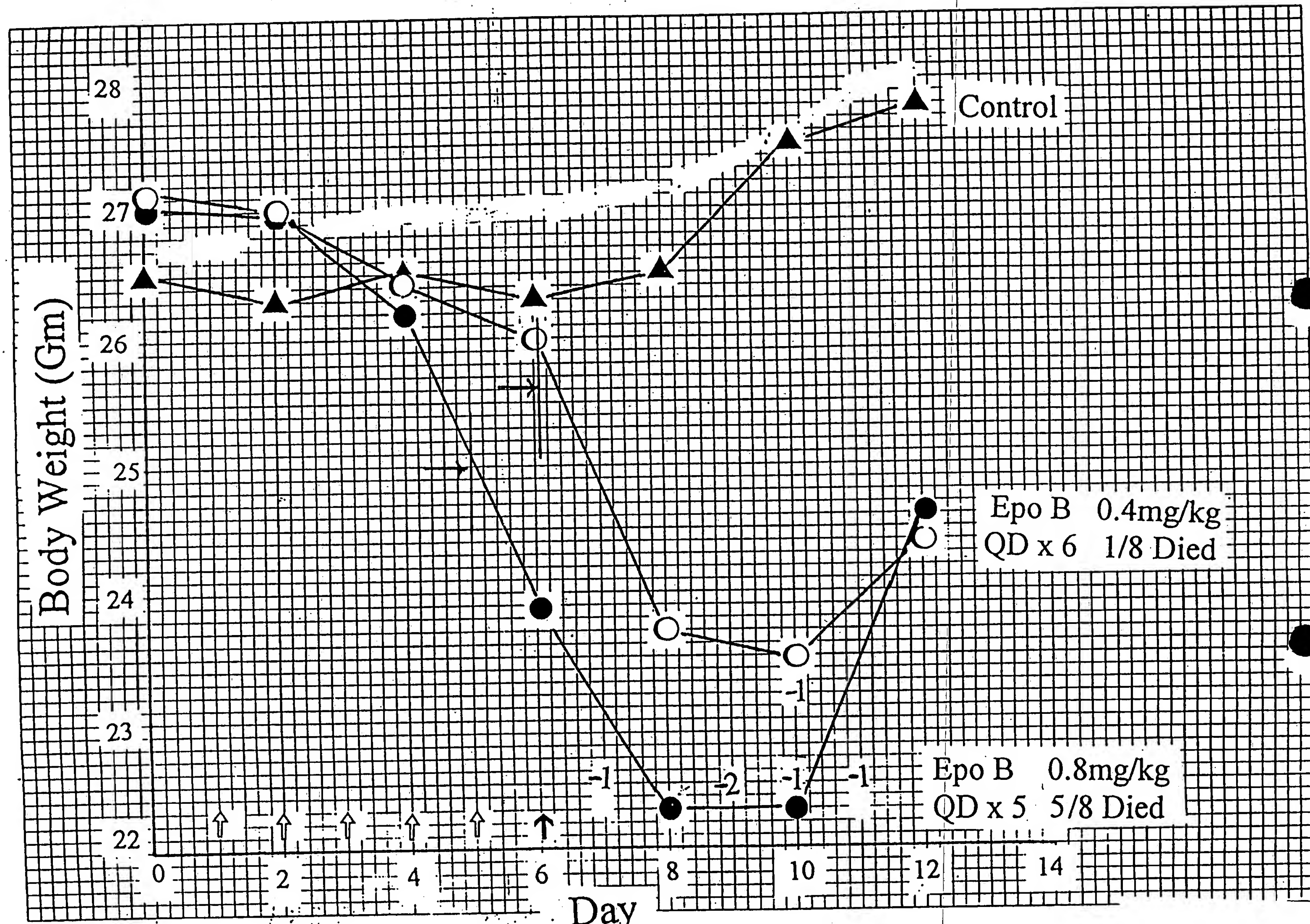


2500
2000
1500
1000
500
0
Tumor Size (mm3)
8
11
12
13
14
15
16
17
Days after Implantation



Body Weight (Gm)
28
27
26
25
24
23
22
0
2
4
6
8
10
12
Day
Control
Desoxyepo B
10mg/kg QD x 8
Desoxyepo B
20mg/kg QD x 6

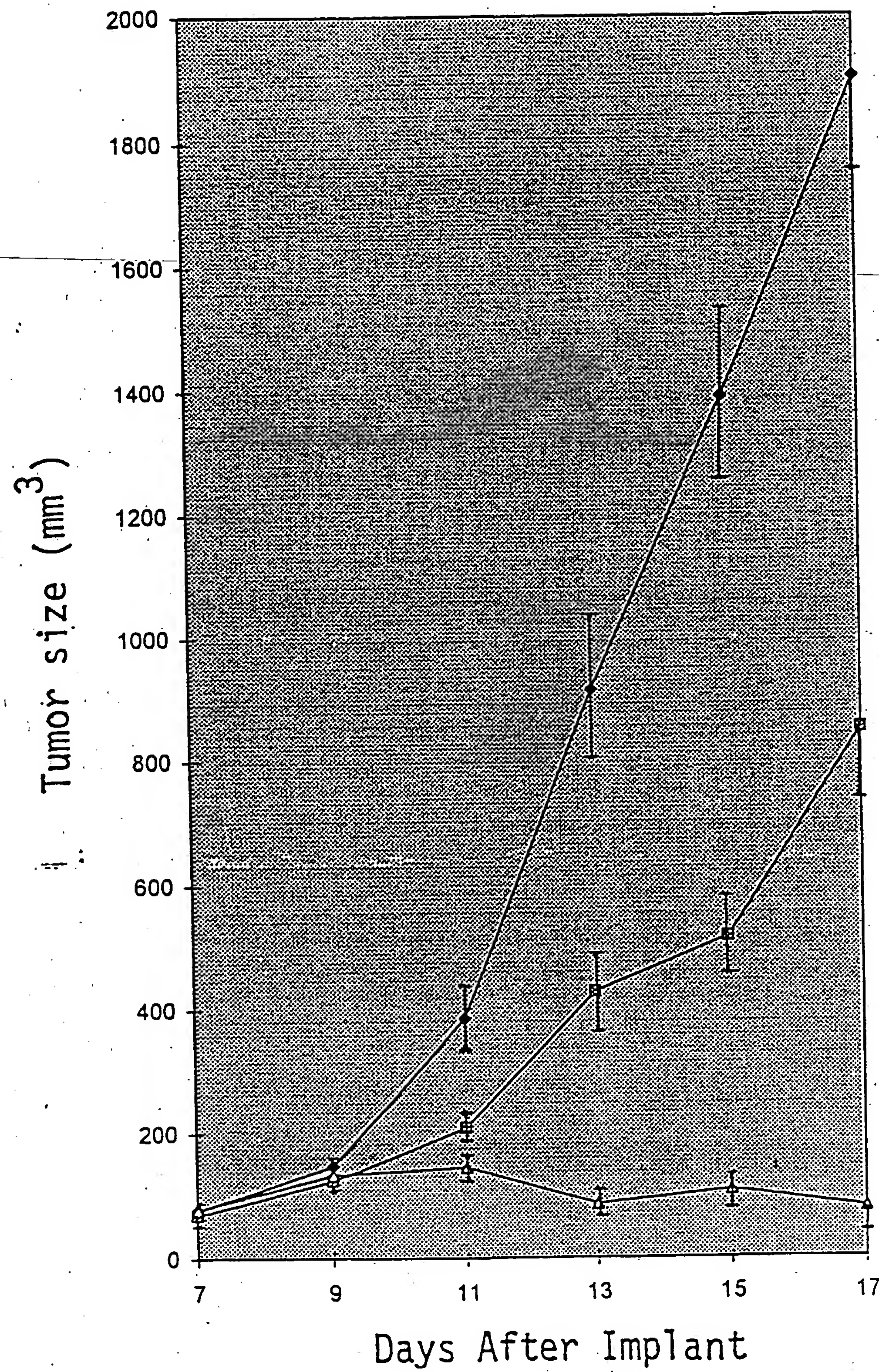
Fig. 44(A)



Body Weight (Gm)
28
27
26
25
24
23
22
0
2
4
6
8
10
12
14
Day
Control
Epo B 0.4mg/kg
QD x 6 1/8 Died
Epo B 0.8mg/kg
QD x 5 5/8 Died
-1
-2
-1
-1
-1

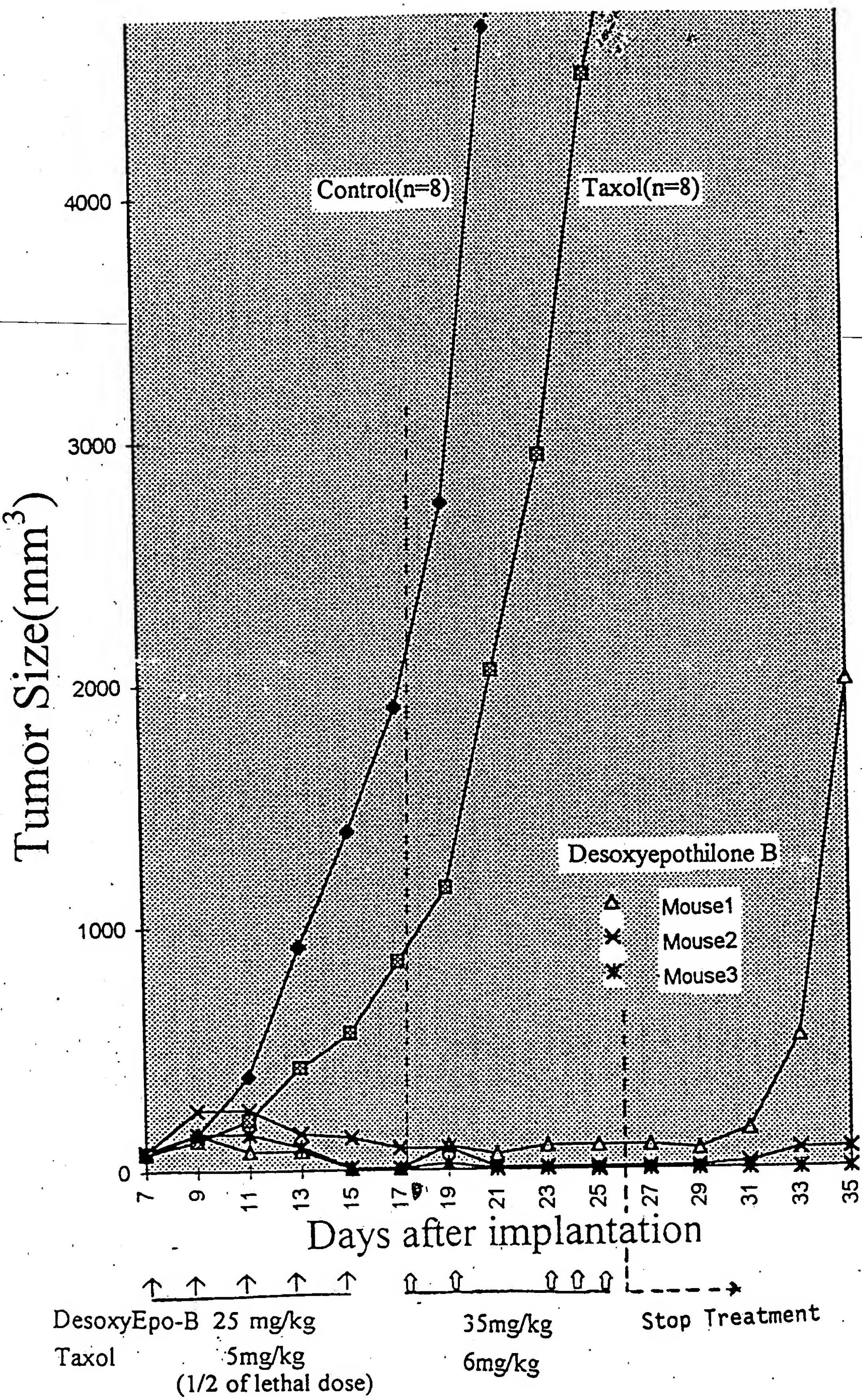
Fig. 44(B)

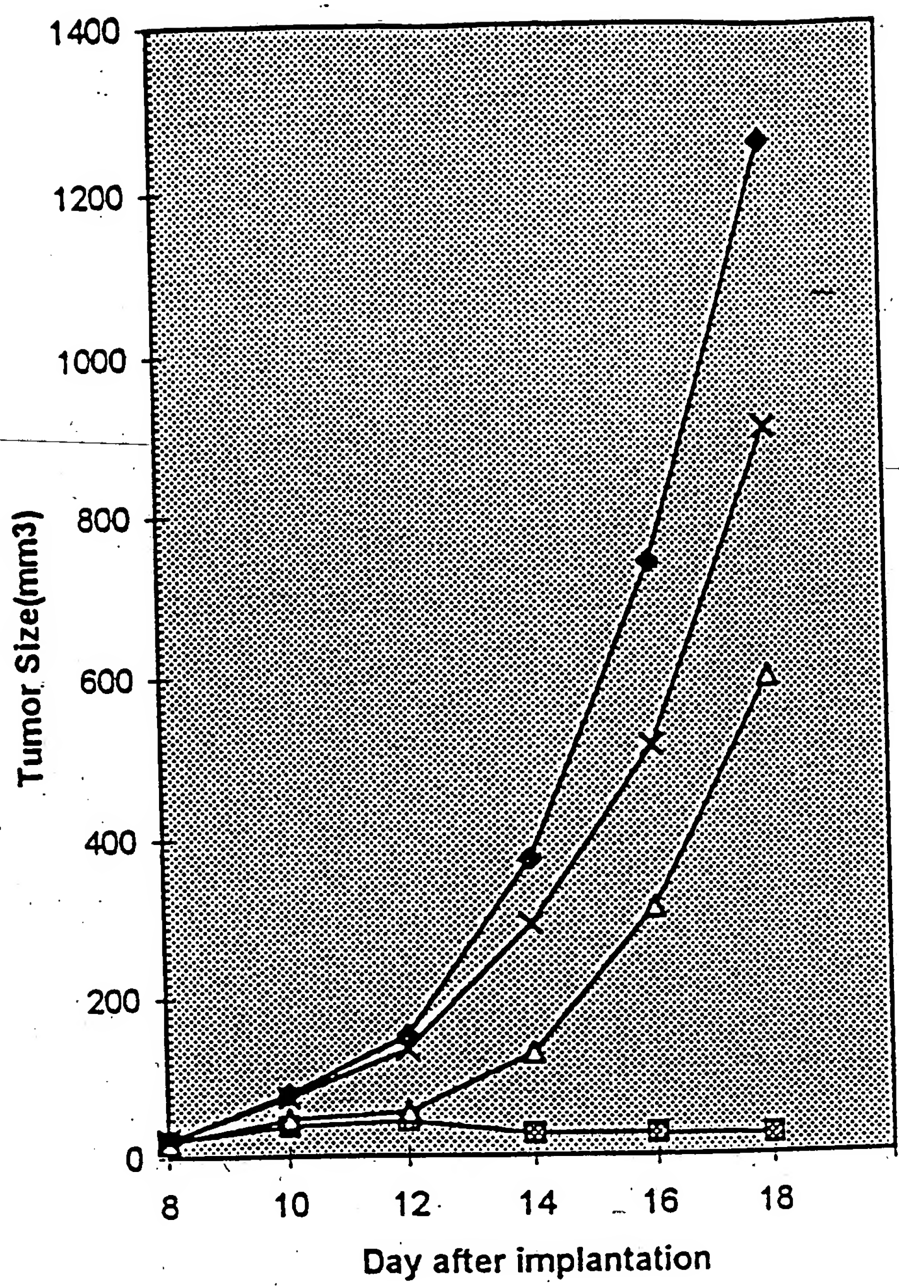
Fig. 45(A)



2000
1800
1600
1400
1200
1000
800
600
400
200
0
Tumor size (mm^3)
7
9
11
13
15
17
Days After Implant

Fig. 45(B)

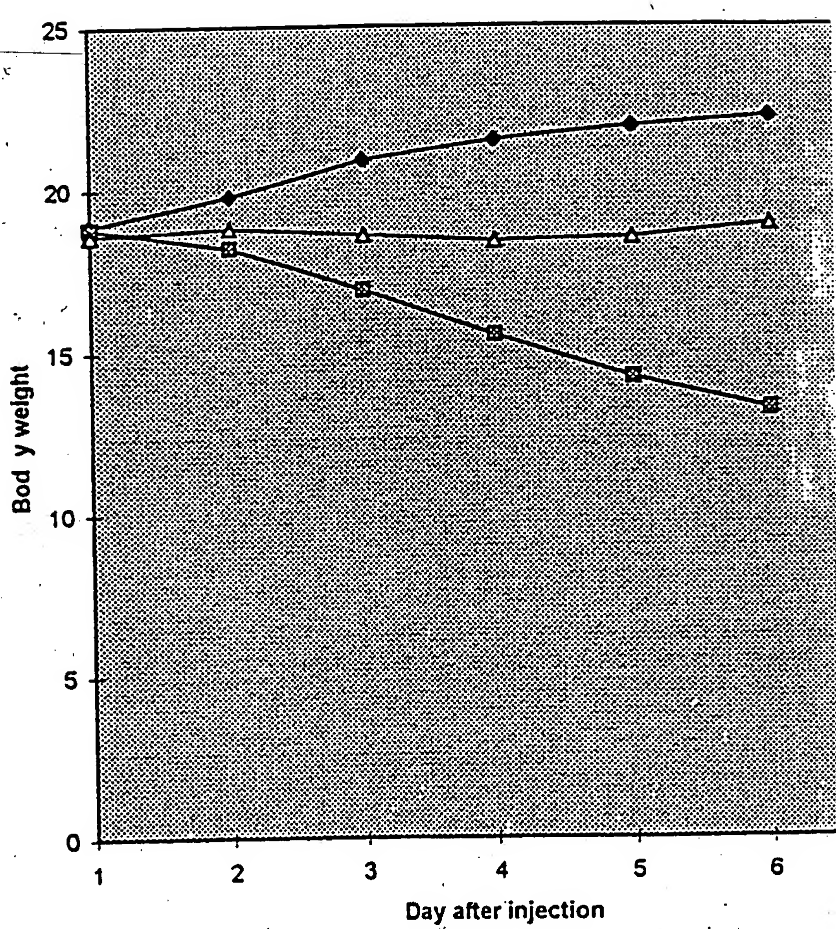

Control(n=8)
Taxol(n=8)
Desoxyepothilone B
Mouse1
Mouse2
Mouse3
Tumor Size(mm^3)
4000
3000
2000
1000
0
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
Days after implantation
DesoxyEpo-B 25 mg/kg
Taxol 5mg/kg
(1/2 of lethal dose)
35mg/kg
6mg/kg
Stop Treatment



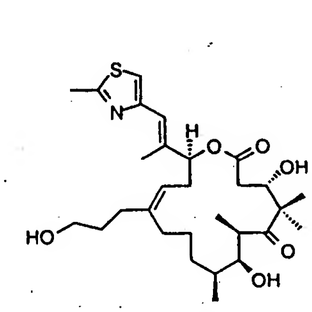
1400
1200
1000
800
600
400
200
0
Tumor Size(mm3)
8
10
12
14
16
18
Day after implantation

Fig. 46

Fig. 47



400 MHz, cdcl3, rt.



43

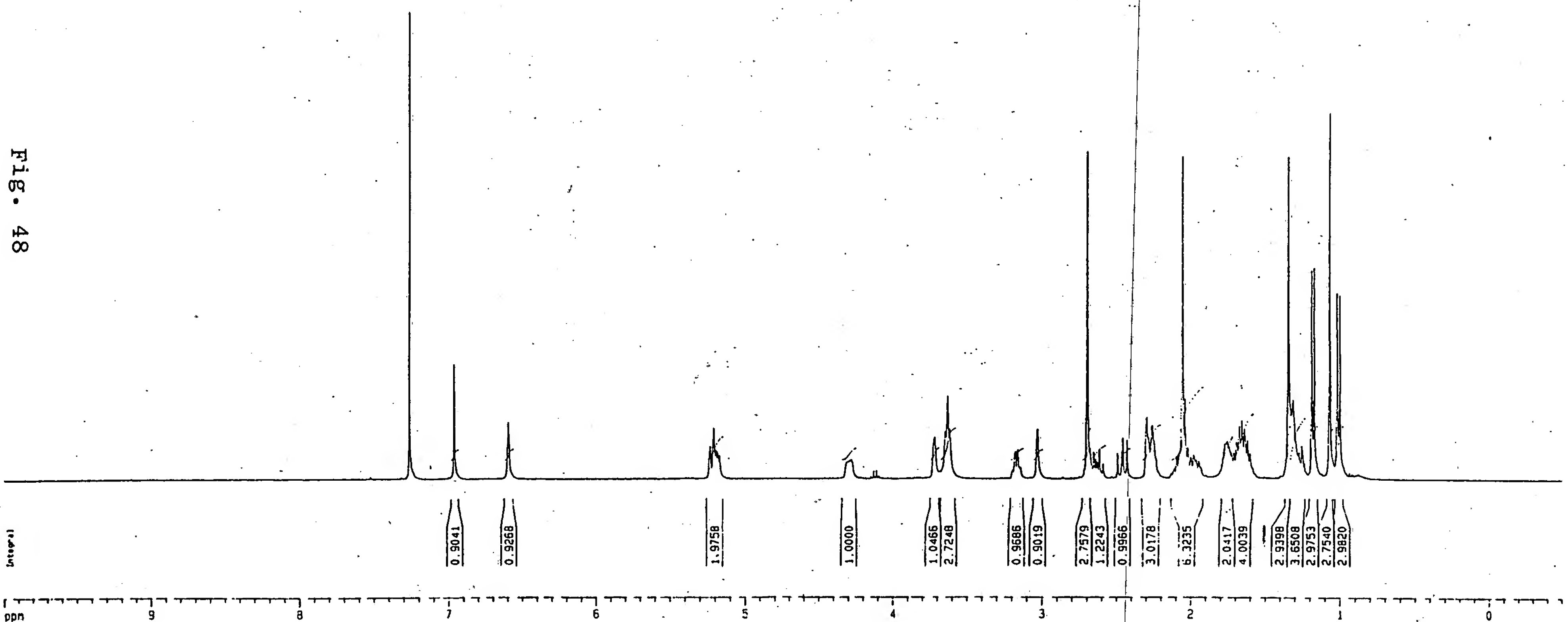


Fig. 48

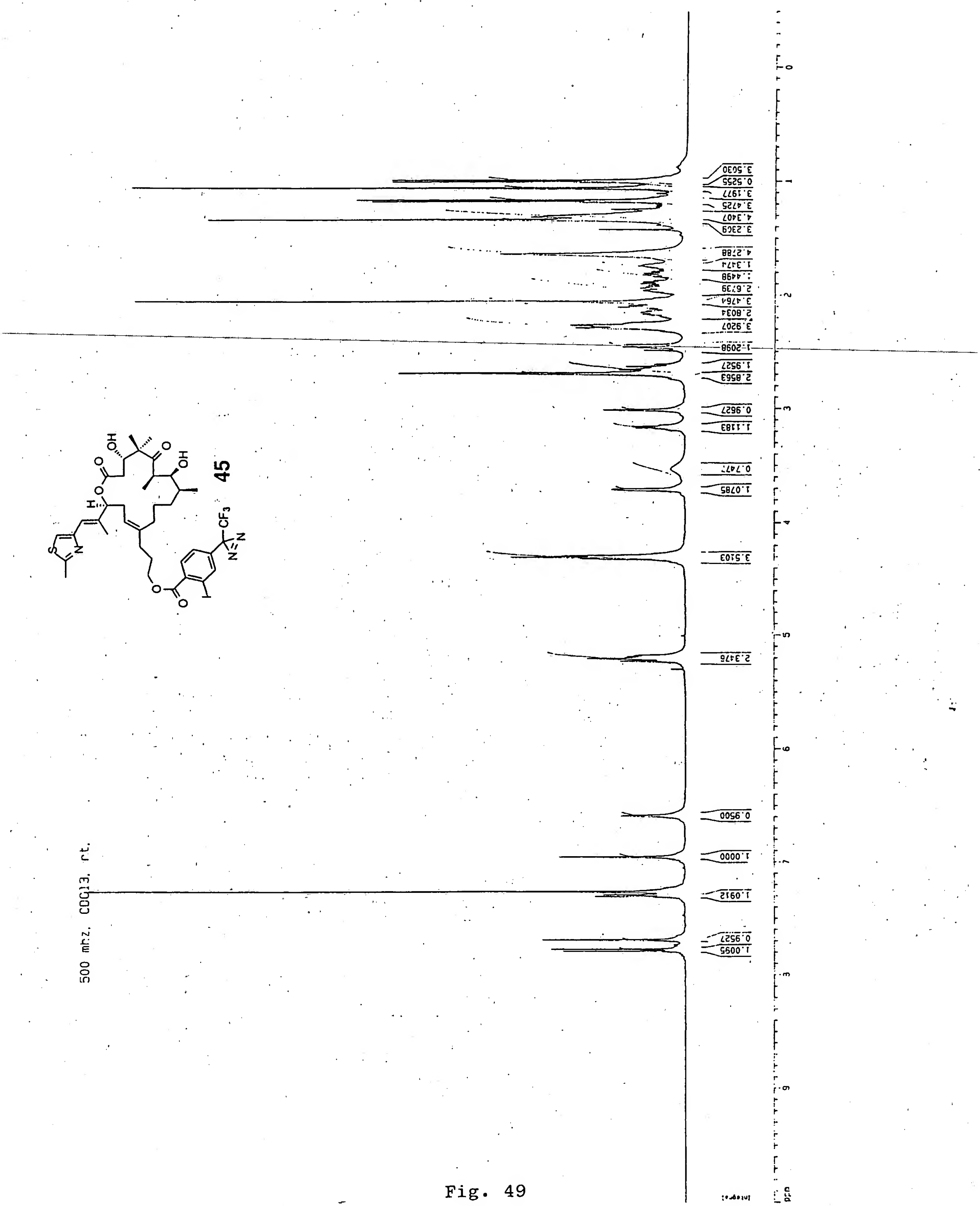
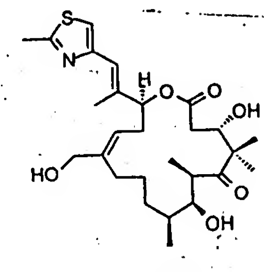

500 mhz, CDCl3, rt.
45
3.5030
0.5255
3.1977
3.4725
4.3407
3.2369
4.2788
1.3474
2.6739
3.4764
2.8034
3.9207
1.2098
1.9527
2.8563
0.9627
1.1183
0.7477
1.0785
3.5103
2.3476
0.9500
1.0000
1.0912
0.9527
1.0095
ppm

Fig. 49

400 MHz, cdcl3, rt.



46

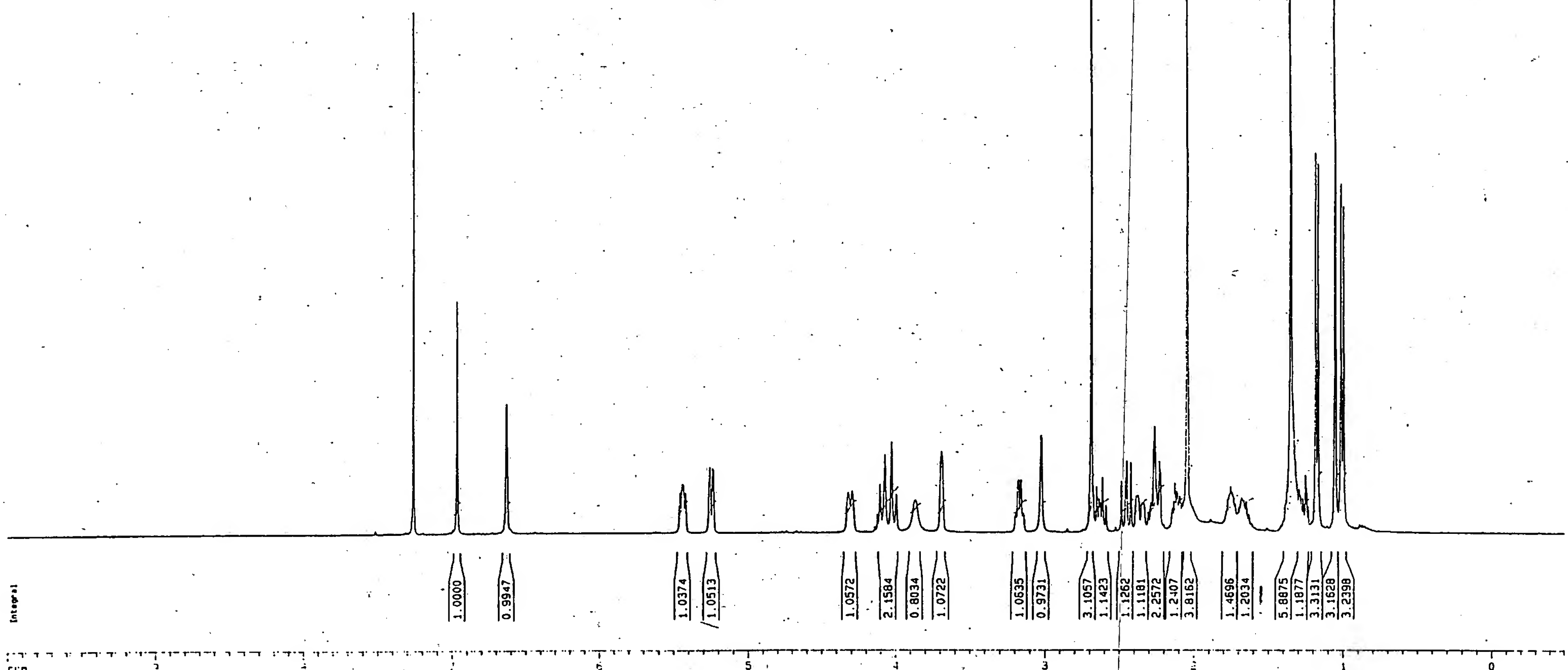
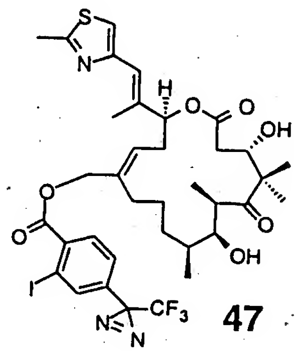


Fig. 50



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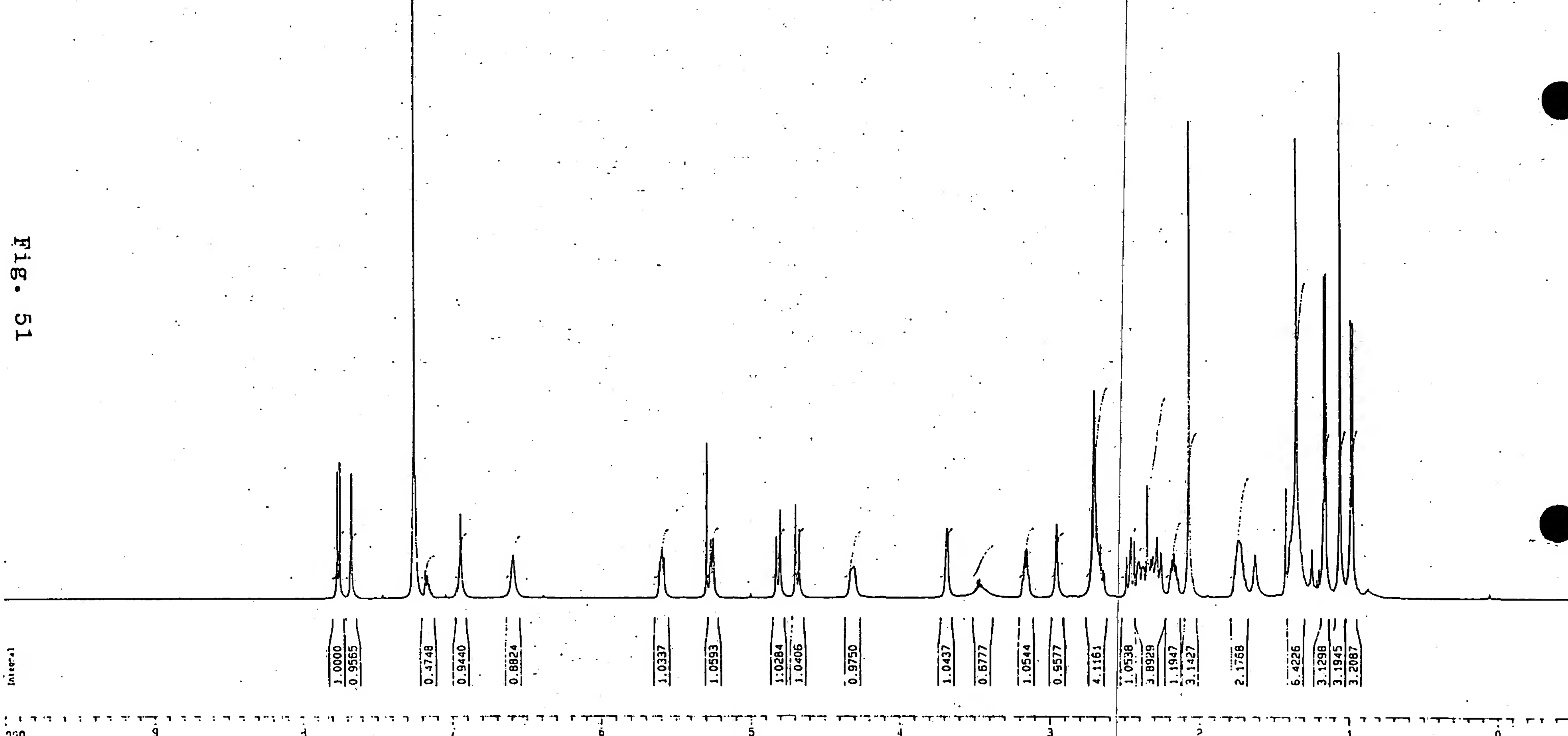

Fig. 51

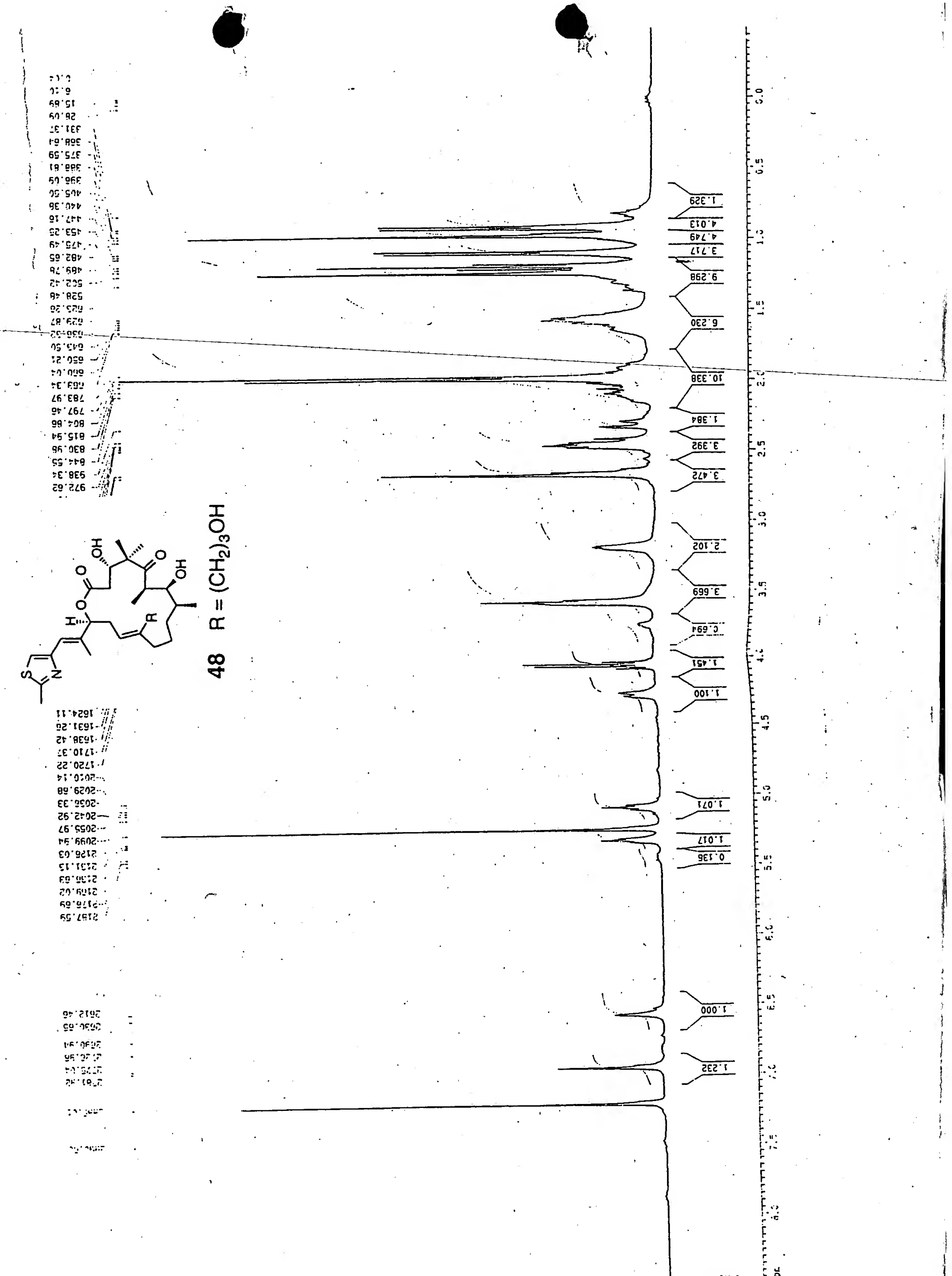

Fig. 52